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**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.01/A1

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** Keio University Global Science Campus program supported by Japan Science and Technology Agency.

**Title:** RNA-binding protein Musashi1 inhibits let-7 miRNA activity in neural stem/progenitor cells

**Authors: *K. KUSANO**[1,3], T. IMAI[1,2], H. KAWAHARA[4], H. INOUE[1], H. OKANO[2]
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**Abstract:** Musashi is an evolutionarily conserved family of RNA-binding proteins that is expressed in the nervous system. In *Drosophila*, this protein plays an essential role in regulating the asymmetric cell division of sensory organ precursor cells through the translational regulation of target mRNA. Its mammalian homologue, Musashi-1, is a neural RNA-binding protein that is expressed in fetal and adult neural stem/progenitor cells (NS/PCs). Transcripts of *m-numb* and *p21$^{waf1}$* were identified as target of Musashi-1, and were repressed their translation by Musashi-1. Previously we reported Musahi1 also interacts with Lin-28 and down-regulates mir98 miRNA processing. Recently, we found that Musashi1 directly and specifically bound to mature *let-7* microRNA *in vitro* and *in vivo*. Their sequences are highly conserved among many species from *Drosophila*, *C. elegans* to human. The *let-7* function is known as translational repression of downstream target gene through Ago2-containing RISC (RNA induced silencing complex). In mammalian cells, *myc*, *ras*, and *hmga2* are known as targets of *let-7* miRNA. We measured *let-7* activities in various cells by using combinatorial Luciferase reporter containing *let-7* complementary sites. As a result, in Msi1-positive human NS/PCs and mouse P19 EC cells, *let-7* activities were relatively low. However, they were relatively high in Msi1-negative cell or the cell that Msi1 content was low. Interestingly, ectopic Msi1 expression in the Msi1-negative cells reduced *let-7* activity. Collectively, in NS/PCs, Msi1 co-existing with Ago2 complex is likely to regulate the activity of *let-7* miRNA at both *let-7* biogenesis and post processing level.

**Disclosures: K. Kusano:** None. **T. Imai:** None. **H. Kawahara:** None. **H. Inoue:** None. **H. Okano:** None.

**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.02/A2

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** ISSSTE Grant RPI-010.2015

**Title:** Intrauterine and neonatal undernourishment deregulate microRNAs that controlling genes transcription that promote to proliferation, development and migration of the oligodendrocyte

**Authors: P. RAMÍREZ-OROZCO**[1], M. LARA-LOZANO[2], J. C. GUADARRAMA-OLMOS[2], I. JIMÉNEZ-ESTRADA[2], M. GONZÁLEZ-MAYA[3], *J. A. GONZALEZ-BARRIOS[4]
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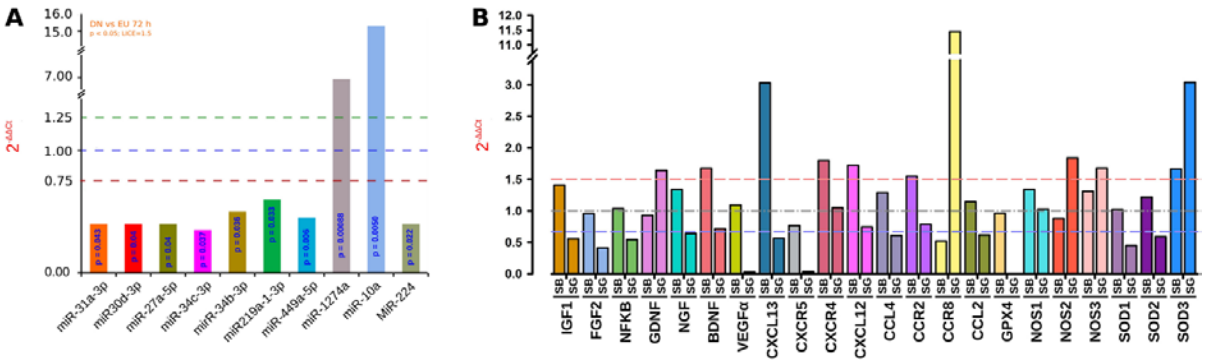
**Abstract:** Nutritional deficiency during pregnancy leads to intra-uterine growth deficiency, affecting the development of fetal cells especially those of the central nervous system. Myelination defect is a common feature of fetal growth restriction in maternal undernourishment, due to a deficit of myelination and a disturbance of oligodendroglial maturation induced by: arrested maturation of the oligodendroglial lineage, increased apoptosis of immature oligodendrocytes, and decreased proliferation of oligodendrocyte progenitors. However, the molecular mechanisms that underlie these phenotypes remain unknown. The mirnome and chemotactic transcriptome of white and grey matter of male pups with intrauterine undernourishment was analysed by qPCR using TLDA technology and individual Taqman probes, the differences were compared to intrauterine well nourished male pups. We found that intrauterine undernourishment decreased the expression of: rno-miR-31a-3p ($p = 0.043$), rno-miR-30d-3p ($p = 0.04$), rno-miR-27a-5p ($p = 0.04$), rno-miR-34b-3p ($p = 0.036$), rno-miR-34c-3p ($p = 0.037$), rno-miR-219a-3p ($p = 0.033$), rno-miR-224 ($p = 0.0224$) and rno-miR-449a-5p ($p = 0.006$) and increased rno-miR-1274a ($p = 0.008$) and rno-miR-10a# ($p = 0.005$) in the white matter, these changes correlate with the gene transcription increase of: IGF-1, BDNF, CXCL13, CXCL12, CCL4, CXCR4, CCR2, NOS1, NOS3, SOD1, SOD3 and decreased of the CXCR5, NOS2 and CCR8 transcription. While in the gray matter the transcription of: GDNF, CCR8, SOD3, NOS2 and SOD3, increased, and the transcription of: NFκB, NGF, IGF1, FGF2, VEGF, CCL4, CXCL13, CCR2, CXCL3, CXCL2, CXCR5, SOD1 and SOD2 decreased. These results show that the mirnome dysregulation is the main target of intrauterine undernourishment causing the development of myelination defects. This study highlights the role of mirnome in the regulation of proliferation, development and chemotaxis of the oligodendrocytes.




**Disclosures:** **P. Ramírez-Orozco:** None. **M. Lara-Lozano:** None. **J.C. Guadarrama-Olmos:** None. **I. Jiménez-Estrada:** None. **M. González-Maya:** None. **J.A. Gonzalez-Barrios:** None.

**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.03/A3

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** FEDER BFU2011-27326

Red TERCEL RD12/0019/0024

Generalitat Valenciana: PROMETEO II/2014/014

**Title:** The hippocampal neurovascular niche development is affected in fgfr1 mutant mice

**Authors: R. GARCIA-LOPEZ**[1], A. POMBERO[2], A. ESTIRADO[2], *S. MARTINEZ[3]
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**Abstract:** Neurogenesis is a basic process occurring during embryonic development that proceeds throughout the adult life in the neurogenic areas, such as subventricular zone and the subgranular zone of the dentate gyrus in the hippocampus. Similar with neurogenesis, the vascular system develops during embryogenesis and continues in the adult dentate gyrus. In addition, neurogenesis and angiogenesis share molecular signals and are mutually promotive. These parallel and depending processes support the concept of neurogenic niche in the brain which proposes a functional unit between the precursor cells and their local microenvironment. Neural stem cells (NSCs) in the neurogenic areas proliferate in groups close to the perivascular space where their self-renewal and differentiation is regulated. Hippocampal neurovascular regulatory system include both diffusible signals and direct contact with endothelial cells and pericytes.,These microenvironmental niche signals include a number of growth factors such as

vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF, also called FGF2). Previous studies suggested that both vascular cells and glial cells may serve as a niche for NSCs. Since both cell types express VEGF and bFGF, these two growth factors may serve as niche signals for NSCs. In the hippocampus, VEGF stimulates the expansion of NSCs and neurogenesis. There are a number of observations suggesting that bFGF may also modulate neurogenesis. It has been reported that knocking out bFGF during critical periods of brain development produces a decrease of neural proliferation and subsequent neuronal differentiation. Interestingly, hippocampal neural precursors express Fgfr1, the major receptor for bFGF and its absence leads to a decrease in neurogenesis accompanied by a severe impairment of long-term potentiation and memory consolidation. We propose to describe the neurogenesis and angiogenesis crosstalk in the dentate gyrus of Fgfr1 mutant mice. In order to address it, we focused on pericytes and endothelial cells to detect vascular abnormalities due to decrease of neural proliferation in this mouse model. We are interested in asses of the potential role of VEGF and bFGF to test the hypothesis that these molecules coordinately regulate the hippocampal neurovascular niche.

**Disclosures: R. Garcia-Lopez:** None. **A. Pombero:** None. **A. Estirado:** None. **S. Martinez:** None.

**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.04/A4

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** Intramural Research Program of NICHD

**Title:** An embryonically expressed 40kD Carboxypeptidase E variant regulates gene expression and neuronal proliferation

**Authors: *L. XIAO**, X. YANG, Y. LOH
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**Abstract:** Carboxypeptidase E (CPE), first identified as a prohormone processing exopeptidase, exerts its function by cleaving C-terminal basic residues from peptide hormones. In addition to its enzymatic function, CPE also known as neurotrophic factor-α1, plays an important role in neurodevelopment as a stem cell differentiating factor (Selvaraj et al,2017) and has neuroprotection activity, independent of its enzymatic activity (Cheng et al, 2013). Previous studies have reported a N-terminally truncated 40KD CPE variant, CPE-ΔN, which is highly expressed in embryonic mouse brain, and has neuroprotective activity in embryonic cortical neurons through up-regulation of FGF2 expression (Qin et al,2014). To determine the structure

of 40KD CPE-ΔN mRNA, Northern blotting, RACE assay and DNA sequencing were carried out. Surprisingly, we found that in addition to WT-CPE, there were three CPE-ΔN transcript variants in embryonic mouse brain. By DNA sequencing analysis the mRNA structure of these transcripts were determined, to be 2.0kb, 1.85kb and 1.54kb in size, of which the 1.85kb was the most abundant. Bioinformatics analysis revealed that the 1.85kb CPE-ΔN has a 1092bp open reading frame (ORF), encoding the 40KD CPE-ΔN protein (364 amino acid). The 1.85kb CPE-ΔN transcript was mainly expressed in the embryonic mouse brain with a peak of expression in E10.5 and then decreased after P1; in contrast, in adult organs such as liver, lung, heart and hippocampus, only WT-CPE was observed. Western blot showed similar pattern of changes of 40KD CPE-ΔN protein during embryonic development. To study whether 40KD CPE-ΔN has effects on regulating genes that are critical for embryonic neurodevelopment, we carried out a microarray analysis on HCC cells, a cancer cell line transfected with mouse CPE-ΔN plasmid. Death associated protein (DAP), Ephrin A1 (Efna1), insulin-like growth factor binding protein 2 (IGFBP2), and Eukaryotic translation initiation factor 4 G (ELF4G) mRNA were up-regulated and they were selected for further study. qRT-PCR results confirmed that transfection of 40KD CPE-ΔN into HT22 cells, a hippocampal cell line induced an increase in DAP, EFNA1, IGFBP2 and ELF4G transcription significantly. MTT assay showed 40 KD CPE-ΔN enhanced the proliferation of HT22 cells. These findings indicate a function of 40KD CPE-ΔN on gene regulation and neuronal proliferation and hence an important player in embryonic neurodevelopment.

1. Selvaraj P, Xiao L, Lee C, Murthy SR, Cawley NX, Lane M, Merchenthaler I, Ahn S, Loh YP. Stem Cells. 2017 35(3):557-571. 2. Cheng Y, Cawley NX, Loh YP.PLoS One. 2013 15;8(8). 3. Qin XY, Cheng Y, Murthy SR, Selvaraj P, Loh YP. PLoS One. 2014 26;9(11)

**Disclosures: L. Xiao:** None. **X. Yang:** None. **Y. Loh:** None.

**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.05/A5

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** Grants-in-Aid 15H05872

Grants-in-Aid 17H04025

AMED Grant 17ek0109120h0003

Salt Science Grant 1736

**Title:** Prenatal stress on Gad1-heterozygotes perturbs GABAergic neurogenesis, GABAergic synapse formation and behavioral phenotypes

**Authors: *A. FUKUDA**[1], T. WANG[1], A. SINHA[1], Y. YANAGAWA[2], T. KAWAI[3], K. HATA[3]
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**Abstract:** Exposure to prenatal stress (PS) and mutations in *Gad1*, which encodes the GABA synthesizing enzyme glutamate decarboxylase (GAD) 67, are both risk factors for psychiatric disorders. In addition, disturbance of PV-positive GABAergic interneurons in the medial prefrontal cortex (mPFC) and hippocampus (HIP) has often been observed in schizophrenia and autistic patients. To elucidate their relationship, we examined GAD67-GFP knock-in mice ($GAD67^{+/GFP}$) that underwent PS from embryonic day 15.0 to 17.5. Administration of BrdU revealed that neurogenesis of GABAergic neurons was significantly diminished in fetal brains during PS. Postnatally, the density of PV-positive, but not PV-negative, GABAergic neurons was significantly decreased in the mPFC, HIP and somatosensory cortex of $GAD67^{+/GFP}$ mice. By contrast, neither wild type (WT) litter mates underwent PS nor naive $GAD67^{+/GFP}$ offspring showed these finding, suggesting that PS in addition to *Gad1* anomaly could specifically disturb the proliferation of neurons destined to be PV-positive (Uchida et al., *Transl. Psychiatry* 2014). Interestingly, comparison of behavioral tests in 4 groups (i.e., WT-PS, WT-naive, $GAD67^{+/GFP}$-PS, $GAD67^{+/GFP}$-naive) indicated anomalous phenotypes only in $GAD67^{+/GFP}$-PS, supporting above hypothesis. Then we are interested in how the double hits by PS and *Gad1* heterologous deletion affected neurogenesis and behavior. We found multiple genes related to neurogenesis and/or neural migration were either hyper-methylated or hypo-methylated in $GAD67^{+/GFP}$-PS. So we have examined expressional alterations of those genes by means of microarray analysis. We also found expression of fukutin (*Fktn*) responsible for Fukuyama type congenital muscular dystrophy was suppressed. Since fukutin glycosylates α-dystroglycan (α-DG) which is associated with GABAergic synapses, we examined glycosylation of α-DG and found it decreased. α-DG is reported to promotes plasticity of GABAergic synapses, so that we examined GABAergic IPSCs. We found that frequency of miniature IPSCs were significantly decreased in the mPFC. These findings may provide new insights into underlying mechanisms of the pathogenesis of psychiatric disorders.

**Disclosures:** **A. Fukuda:** None. **T. Wang:** None. **A. Sinha:** None. **Y. Yanagawa:** None. **T. Kawai:** None. **K. Hata:** None.

**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.06/A6

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** BBSRC Bb/N006542/1

**Title:** Tissue-specific regulation of gene expression by Pax6 in the developing mouse forebrain

**Authors: *Z. KOZIC**, I. QUINTANA-URZAINQUI, D. J. PRICE
Ctr. for Integrative Physiol., Univ. of Edinburgh, Edinburgh, United Kingdom

**Abstract:** The development of complex forebrain structures is under the strict regulation of multiple molecular networks, which are controlled by a relatively small group of transcription factors. During embryonic development, the forebrain vesicle expands to form two telencephalic vesicles which surround the inner structure, the diencephalon. In later stages the telencephalon will form the cerebral cortex and basal ganglia, while the most notable diencephalic structure is the thalamic complex.
Pax6 is a high-ranking, pleiotropic transcription factor with an important role in the development of the neural system. It is a member of the Paired-box (Pax) family of transcription factors, known for containing both a paired domain and a homeodomain. Because of its key role in multiple processes in neural development, Pax6 has become one of the most studied members of the Pax family. Such processes include neurogenesis, neural patterning and differentiation, cell migration and axon growth and guidance. Pax6 mutations are known to cause aniridia in humans and the small eye phenotype in mice, where defects in forebrain structures and failure in forming thalamocortical connections have been observed. Therefore, its activity is well studied in the eye and the cortex, but little is known about its exact regulatory role in the diencephalon, where high levels of Pax6 expression have also been reported, especially in the prethalamus.
We performed a series of RNA-sequencing experiments coupled with computational analysis to detect genome-wide changes in gene expression in the developing cortex and diencephalic tissues after acute, tamoxifen-induced deletion of Pax6, and we identified a large number of genes with significantly altered expression levels after Pax6 deletion. Comparison of these effects across the cortex, prethalamus and thalamus has shown a major contrast in the direction of differential expression between the cortex and diencephalic tissues. The enrichment analysis of functional terms and pathways has shown a similar pattern, with groups of genes involved in certain processes being regulated in opposite directions between the cortex and the diencephalon. One example is the cell cycle where, after deletion of Pax6, many genes are upregulated in the cortex while a significant number of genes experience downregulation in the diencephalon. We present our findings, providing insight on how highly conserved transcription factors can exert their regulation in different, context-specific ways.

**Disclosures: Z. Kozic:** None. **I. Quintana-Urzainqui:** None. **D.J. Price:** None.

**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.07/A7

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** ANSEF 2016, biochem 4414

**Title:** The sole role of PRPS-1 in the regenerative processes after experimental stroke

**Authors: *K. DANIELYAN**[1], R. D. VARDANYAN[2], A. SIMONYAN[3], A. S. SAGYAN[2]
[1]H. Buniatian Inst. of Biochem., Yerevan, Armenia; [2]YSU, Yerevan, Armenia; [3]H Buniatian Inst. of Biochem., Yerevan, Armenia

**Abstract: Background.** Phosphoribosylpyrophosphate synthetase-1 (PRPS; EC 2.7.6.1) is the widely distributed in the human tissues and servs as a regulative key enzyme for purine metabolism (Becker and Kim, 1987), whereas Xanthine Oxidase (XO; EC 1.1.3.22) is the enzyme responsible for the catabolism of purine nucleotides and might coordinate by feed-back mechanism this entire biochemical pathway (Danielyan, K.E., 2011). We proposed, activation of PRPS-1 and simultaneous inhibition of XO might initiate regenerative processes after stroke. **Methods.** We have used hydrogen peroxide intracranial injection (3%) as the model for the ROS generation phase of stroke development. XO activity was measured by evaluation of uric acid formation. PRPS-1 was measured by the kit (Novocib, France). BBB (Blood Brain Barrier) integrity was evaluated by utility of Evans Blue. ANOVA one way analysis was used for evaluation of statistical significance of the results. KI-67 was used for detection of cells proliferation in the specific areas. **Results.** PRPS-1 activity after stroke in rats was stimulated by phosphates (control; 1.9145±0.0400 vs phosphates treatment 6.6304±0.0500 vs allopurinol treatment 1.6921±0.0359, $p<0.05$). In phosphate treated group in comparison with the control XO activity was lower (control; blank - 0.6406±0.0378; substrate - 0.8513±0.1527; phosphate treatment group blank - 0.2500±7.5758e-3 vs substrate 0.3314±0.0625; allopurinol treated group: blank - 0.5549 ±8.1301e-3 vs substrate 0.5786±0.017). Ki-67 incorporation was more pronounced in phosphate treated group in comparison with the control. BBB disruption was less in experimental vs control group. **Conclusion.** Phosphates are proposed to be used as the poststroke regenerative agents.

**Disclosures: K. Danielyan:** None. **R.D. Vardanyan:** None. **A. Simonyan:** None. **A.S. Sagyan:** None.

**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.08/A8

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** ABRC (ADHS-14-082982)

UA intramural funds

**Title:** Enhanced Nrf2 expression improves neural stem cell function during a critical aging period

**Authors: *A. ANNADURAI**[1], M. J. CORENBLUM[1], S. RAY[2], K. KIRWAN[2], A. REED[2], C. A. BARNES[3], L. MADHAVAN[1]
[1]Dept. of Neurol., [2]Neurosci. and Cognitive Sci. Undergraduate Program, [3]Departments of Psychology and Neurosci., Univ. of Arizona, Tucson, AZ

**Abstract:** Our recent studies have examined the function of rat subventricular zone (SVZ) neural stem and progenitor cells (NSPCs) during aging. This work indicates that although NSPC function continuously declines with advancing age, there is a critical time period during middle-age (13-15 mos) when a prominent reduction in NSPC survival, regeneration, and associated behavioral function (fine olfactory discrimination), occurs. We also find that this specific temporal pattern of NSPC deterioration is mediated via the reduced expression of the redox-sensitive transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Based on these data, in this study, we investigated whether increasing Nrf2 expression could potentially mitigate the decline in NSPC function across the identified critical middle-age period. First, we generated recombinant adeno-associated viral (rAAV2/1) vectors, to overexpress Nrf2 within endogenous NSPCs in the aging SVZ niche, and characterized their efficiency. Subsequently the Nrf2 vectors (or eGFP vectors as controls) were administered into the SVZs of aging rats, at time-points either before or after the critical period. Results indicate that animals that had received rAAV2/1-Nrf2-eGFP, before the advent of the critical middle-age period (at 12 mos), exhibited substantially improved fine olfactory discrimination abilities in comparison to animals receiving the control rAAV2/1-eGFP virus. Striatal function, measured via a beam task, was also enhanced in the Nrf2 overexpressing animals compared to controls. Additionally, histological analysis revealed that NSPC survival, proliferation, and neurogenesis in the SVZ had significantly increased upon Nrf2 overexpression. Early data also show greater NSPC migration through the rostral migratory stream, and their subsequent integration into the olfactory bulb, in Nrf2 overexpressing rats. On the other hand, Nrf2 overexpression in SVZ NSPCs after the completion of the critical period (at 21 mos) did not result in a significant improvement of NSPC activity at either cellular or behavioral levels. In summary, these data support Nrf2 pathway modulation as a potential

approach to enhance aging NSPC function, and have important implications towards developing stem cell-based therapeutics for age-related neurological disorders.

**Disclosures: A. Annadurai:** None. **M.J. Corenblum:** None. **S. Ray:** None. **K. Kirwan:** None. **A. Reed:** None. **C.A. Barnes:** None. **L. Madhavan:** None.

**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.09/DP01/A9 (Dynamic Poster)

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** NIH Grant MH101188

NIH Grant OD011107

**Title:** Microglial cells intimately interact with multiple cell types in the proliferative zones of the fetal primate cerebral cortex

**Authors: *S. C. NOCTOR**[1], A. F. TARANTAL[2], N. BARGER[3]
[1]Psych & Behavioral Sci., UC Davis, Sacramento, CA; [2]California Natl. Primate Res. Center, Departments of Pediatrics, Cell Biol. and Human Anat., UC Davis, Davis, CA; [3]Univ. of California, Davis - MIND Inst., Sacramento, CA

**Abstract:** Microglia, the brain's immune cells, participate in normal developmental processes in the brain, in addition to immune functions. We have shown that microglia phagocytose neural precursor cells (NPCs), including radial glia and intermediate progenitor cells, in the fetal cerebral cortex. Our previous work identified microglia and NPCs by immunolabeling microglia with the Iba1 antibody, and NPCs with the cell specific antibodies Pax6 and Tbr2. Iba1 immunostaining labels the soma and processes of microglial cells, but Pax6 and Tbr2 label only the nuclei of NPCs. To better understand cellular interactions between microglia and fetal cortical cells, we labeled the entire cell body and cellular processes of fetal cortical cells with EGFP. We performed ultrasound guided *in utero* intracerebral injections of a lentiviral vector in fetal rhesus macaque on gestation day 85. Tissue was harvested 5 days later, brains sectioned at 100 microns, stained with cell specific antibodies (Radial glia: Pax6 and GFAP; Intermediate progenitor cells: Tbr2; Microglia: Iba1; Mitotic cells: 4A4; Cell nuclei: DAPI), and imaged with epifluorescent and confocal microscopes. In addition to phagocytosis, we find that microglial cells intimately contact radial glia. A single radial glial cell and its cellular processes are contacted by and enveloped by multiple microglia at several points between the ventricle and the pia. Microglia contact the soma and cellular processes of radial glia in all phases of the cell cycle, and make similar contacts with intermediate progenitor cells and migrating neurons. We

also show that individual microglia interact with more than one cell at a time: we observed single microglial cells phagocytosing and interacting with multiple cortical cells simultaneously. In addition, microglia exhibit unique morphological features that indicate a correlation with function. For example, microglial cells extend reticulated processes toward NPCs near the surface of the ventricle. The reticulated microglia appear to represent a specific subset of phagocytic cells. Given the multiple roles microglia play in both the immune response and postnatal neuronal development, our current findings expand the repertoire of microglial cells in monitoring, maintaining, and remodeling the neurogenic niche of the fetal primate cerebral cortex.

**Disclosures: S.C. Noctor:** None. **A.F. Tarantal:** None. **N. Barger:** None.

**Poster**

**459. Cell Cycle Mechanisms in Neurogenesis I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 459.10/A10

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** NIH Grant 1U01MH105989-01

EMBO LTF

DFG Fellowship

**Title:** A multimodal single-cell approach identifies intercellular signaling networks in the developing human neocortex

**Authors: *S. MAYER**, J. CHEN, D. VELMESHEV, U. EZE, B. ALVARADO, M. PAREDES, C. E. CUNHA, A. R. KRIEGSTEIN
Regeneration Med., Univ. of California, San Francisco, San Francisco, CA

**Abstract:** We have only just begun to understand the diversity of neural progenitor cells and the differentiation trajectories of postmitotic cells during human neocortical development. Recent advances in single-cell transcriptomics have identified novel molecular markers defining distinct cell types in the developing and adult neocortex. The combination of single-cell transcriptomics with the physiological firing patterns of neurons has revealed a larger diversity of neuronal cell types than previously appreciated. Even though classical synaptic signaling is absent during early stages of brain development, neurotransmitters nonetheless modulate critical aspects of neural progenitor cell proliferation and differentiation, as well as the migration and maturation of newborn neurons. Here we combine single-cell transcriptomics with physiological response characteristics of dissociated cells from the developing human cortex, to achieve a high dimensional characterization of the diverse cell types. We use a high-throughput method to

measure intracellular calcium dynamics in response to a range of neurotransmitters in single cells captured on microfluidic chips. Subsequently, the same single cells are processed for single-cell RNA sequencing. This novel approach enables us to link a cell's physiological response pattern to its molecular profile. We find that different molecularly identified cell types display differential responses to a panel of neurotransmitter receptor agonists and thereby uncover how response patterns change with cellular maturation and differentiation. Interestingly, progenitor cells in the germinal zone respond preferentially to the application of purinergic and serotonergic agonists, while postmitotic neurons in the cortical plate respond to the neurotransmitter receptor agonists that target glutamate and gamma amino butyric acid (GABA) receptors. Moreover, serotonergic receptor activation promotes the proliferation of progenitor cells in the late second trimester. The synthesis of the transcriptomic and physiological fingerprints of a cell allows us to start to decipher the signaling pathways that control the cell biology of different cell types in the developing human neocortex.

**Disclosures: S. Mayer:** None. **J. Chen:** None. **D. Velmeshev:** None. **U. Eze:** None. **B. Alvarado:** None. **M. Paredes:** None. **C.E. Cunha:** None. **A.R. Kriegstein:** None.

**Poster**

**460. Migration During Neurogenesis**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 460.01/B1

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** NIH R01 NS082262-01

**Title:** JNK signaling is required for the directed migration of cortical interneurons

**Authors: *S. E. HICKLING**[1,2], A. K. MYERS[2], M. P. WILSON[2], E. S. TUCKER[2]
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**Abstract:** During corticogenesis, inhibitory interneurons must migrate into the developing cortical plate, deposit in the correct cortical layer, and establish connections with their appropriate synaptic partners. Aberrant migration of inhibitory interneurons can alter the formation and function of cortical circuitry and lead to severe neurological disorders including epilepsy, autism and schizophrenia. Cortical interneurons travel tangentially in migratory streams to reach the cerebral cortex and then turn radially to exit migratory streams and invade the cortical plate. Our lab previously found that disruption of the c-Jun N-terminal kinase (JNK) signaling pathway results in a delayed entry of cortical interneurons into the cortex, as well as the premature departure of cortical interneurons from migratory streams. In the current study, we are using live-cell confocal microscopy to explore the mechanisms by which JNK activity

coordinates two cell biological processes that are essential for the guided migration of cortical interneurons: nucleokinesis and leading process branching. Nucleokinesis is a cyclical process whereby the cell bodies of migrating cortical interneurons translocate into a cytoplasmic swelling formed in their leading process. Our data shows that cortical interneurons treated with JNK inhibitor exhibit major deficiencies in nucleokinesis with smaller nuclear translocation distances, as well as shorter extensions of cytoplasmic swellings. These findings suggest that JNK plays a major role in the cellular control of migration through nuclear movement. On the other end of the cell, the leading process is a highly dynamic structure that extends and retracts branches in order to sense and respond to extracellular guidance cues that are located in the environment. Our preliminary data also suggest that JNK-inhibited cortical interneurons display longer leading processes, as well as fewer leading process branches. Together, these data indicate that JNK may be controlling nucleokinesis and branching dynamics to direct the migration of cortical interneurons. In future experiments, we will investigate upstream activators and downstream targets of JNK signaling that enable the guided migration of cortical interneurons. Ultimately, our results will improve our understanding of cortical development and hopefully provide novel insight into the etiology of cortical circuit disorders.

**Disclosures: S.E. Hickling:** None. **A.K. Myers:** None. **M.P. Wilson:** None. **E.S. Tucker:** None.

**Poster**

**460. Migration During Neurogenesis**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 460.02/B2

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** NIH R01 NS082262

**Title:** Elucidating the roles of Jnk1, Jnk2, and Jnk3 in cortical interneuron development

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**Abstract:** The human cerebral cortex functions in a balance between excitation and inhibition. This balance is first established during embryonic development through proper generation, migration, and differentiation of both cortical excitatory neurons and inhibitory interneurons. Disruptions to these key developmental processes can impair cortical function and lead to diseases such as autism, epilepsy, and schizophrenia. During development, interneurons navigate their way through the cortical rudiment by integrating both intracellular and extracellular cues to direct their migration. Our lab has shown a role for the c-Jun N-terminal Kinase (JNK) signaling pathway in cortical interneuron migration. One of the three JNK genes, *Jnk1*, is required for

interneuron entry into the cortex and correct formation of migratory streams. In addition to *Jnk1*, we hypothesize that the *Jnk2* and *Jnk3* genes also play a crucial role in cerebral cortex formation. Accordingly, we developed a conditional triple knockout (cTKO) mouse model where *Jnk1* is deleted from interneurons in mice lacking both *Jnk2* and *Jnk3*. In the current study, we have analyzed *in vivo* cortices ranging from Embryonic Day 13.5 (E13.5) to Postnatal Day 0 (P0). At E13.5, cTKO interneurons are markedly delayed in their entrance into the cortex, have non-tangentially aligned processes, and have large gaps in their migratory streams. At E15.5, interneuron streams are dispersed, and interneurons form clusters in the intermediate zone and nascent cortical plate. In addition, disruptions to cortical excitatory neurons and radial glial scaffolding have also been observed. Cortical excitatory neurons are incorrectly positioned in the developing cortex. Nestin labeling indicates that radial glial end feet are often detached from the pial surface, and their basal processes are frequently misaligned. At P0, disruptions are seen to both interneurons and excitatory neurons. cTKO interneurons have migratory morphologies with radially aligned processes and do not appear to laminate correctly. Additionally, cTKO brains have enlarged ventricles, and a more compact layering of lower-level excitatory neurons. Through further characterization of the cTKO cortex, we will further define the roles of the three JNK genes in excitatory and inhibitory neuron development. Deciphering the genetic regulation of cortical development will help uncover potential causes of neurodevelopmental disorders that impact the assembly and function of cortical circuitry, and can ultimately lead to better treatment of these devastating diseases.

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**Poster**

**460. Migration During Neurogenesis**

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**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** University of Verona DDSP-FUR-6616

**Title:** Meningeal neural precursors contribute to cortical neurogenesis in aging mice

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Belgium; [5]Swiss Federal Inst. of Technol., Lausanne, Switzerland; [6]Dept. of Computer Sci., Univ. of Sheffield, Sheffield, United Kingdom; [7]Dept. of Med. Biotech. and Translational Med., Univ. of Milan, Milan, Italy

**Abstract:** We recently described that meningeal cells are able to migrate to the posterior cortex in the postnatal period, and differentiate into functional neurons that express the marker Satb2. These meningeal neurogenic cells belong to the PDGFRβ$^+$ lineage. By single-cell RNA sequencing analysis, we found in meninges the presence of radial glia-like cells and neuronal cells, and a cell type with an intermediate phenotype representing radial glia-like meningeal cells in their differentiation process (Bifari et al., 2015; Bifari, Decimo et al., 2017). However, whether neurogenic radial glia-like meningeal cells and newly added meningeal-derived postnatal neurons are maintained during aging is not known.With this work, we aimed to investigate the presence of radial glia-like cells in meninges in aging mice and the long-term survival of migrated meningeal cells in the upper layers of the brain cortex. We analysed the expression of the radial glia marker Glast in the meninges of 8, 24 and 40 weeks old mouse brains. We found Glast$^+$ cells in meninges of all analysed stages. At 8 and 24 weeks, Glast$^+$ cells represent ~15-17% of the meningeal cells, while their expression slightly decrease during aging (~12% at 40 weeks).Moreover, meningeal-derived cells in the brain cortex survived up to 1 year after meningeal labelling at P0, showed a similar phenotype compared to meningeal derived neurons in young mice and expressed the neuronal marker Satb2 (~52%). This study underlines the importance of meningeal-derived neurons in aging brain cortex, opening new questions about their role and their functions in the adult/aged brain in health and disease.

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**Poster**

**460. Migration During Neurogenesis**

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**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** Patterson Trust Award Program in Clinical Research

**Title:** Redox dysregulation in the effects of prenatal stress on GABAergic progenitor migration in embryonic brain

**Authors: *J. BITTLE**, H. GION, K. MAPUSKAR, M. MCCORMICK, M. DAILEY, D. SPITZ, H. STEVENS
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**Abstract:** Stress experienced by the mother during pregnancy is associated with an increased risk of psychiatric disorders in her offspring, but the cellular mechanisms by which prenatal stress (PS) affects the developing brain have yet to be identified. Our lab has shown that PS disrupts inhibitory neuron migration and subsequent maturation. The disruption of inhibitory neural circuitry during fetal development can have crucial, long-lasting consequences for neuronal function into adolescence and adulthood. The balance between oxidative and reductive processes is critical during rapid periods of cell growth and differentiation, so small changes in the level of reactive oxygen species (ROS) due to PS could have significant effects on developing GABAergic systems. We used four approaches to investigate redox imbalance as a mechanism for PS effects on GABAergic migration, utilizing a mouse model of repetitive restraint stress starting on embryonic day 12 (E12). First, the administration to pregnant dams of N-acetylcysteine, a common antioxidant supplement, during prenatal stress rescued delay of GABAergic interneuron migration *($p < 0.01$)*. Second, antioxidants were altered by PS in the brain of E13 embryos—thioredoxin reductase (Txnrd) and glutathione peroxidase (GPx). PS led to a decrease in Txnrd ($p$=0.06) enzyme activity level, but an increase in *Txnrd* gene expression ($p$=0.06), and a decrease in GPx *($p$=0.19)* enzyme activity level and gene expression ($p < .05$), suggesting alterations in redox balance. We also found changes in *Sestrin1* and *Sestrin3* gene expression levels. Third, dihydroethidium, a fluorescent indicator of the most common oxygen free radical, superoxide, was increased by 50% ($p$=0.06) in E13 brains of PS embryos, suggesting greater levels of ROS. Fourth, live imaging experiments of embryonic brain slice tissue are ongoing to explore how redox imbalance affects GABAergic cell migration. Using time lapse imaging, we are assessing direction and rate of movement of individual GAD67GFP+ neural progenitors in superficial and deep migratory streams from the medial ganglionic eminence into the neocortex, incubated in either standard artificial cerebral spinal fluid (aCSF) or aCSF with a pro-oxidant, hydrogen peroxide. These experiments together will elucidate the role of oxidative and reductive processes in the effects of PS on GABAergic interneuron migration. Redox dysregulation may play a significant role in the elusive mechanisms by which persistent cellular changes are induced in the developing brain by maternal PS. Knowledge of these mechanisms could lead to novel interventions for those at risk for psychiatric disorders.

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**Poster**

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**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** NIH Grant R01MH091424 to MMM

**Title:** The role of microglia and pia mater in malformations of cerebellar development

**Authors: *S. S. KULKARNI**[1], M. PEREZ-POUCHOULEN[2], M. M. MCCARTHY[2,3], R. L. RAMOS[1]
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**Abstract:** The proliferation and migration of cerebellar neurons and glia are critical to the correct establishment of cerebellar folia and lamina during development, as well as proper functioning of these circuits in adulthood. Previous studies have carefully described the development of nearly all types of cerebellar neurons and glia; however, less is known about pia-associated cells. Using wild-type rats and mice, as well as genetically-engineered mice, we provide novel anatomical data on pia-associated microglia of the cerebellum, which can be identified by several markers including Iba1 and Cx3cr1. Microglia are resident immune cells of the brain and derived from a macrophage lineage. We describe the density and morphology of these cells in the early postnatal cerebellum, a period when granule cells are actively proliferating and migrating. We also document the relationship between pia-associated microglia and malformations of cerebellar development. Namely, neuronal heterotopia consisting of granule cells that failed to migrate were associated with breaches in the pia and the absence of pia-associated microglia. Heterotopias were also characterized by changes in the morphology of Bergman glial fibers as well as in the distribution of proliferating and differentiating granule cells. Our data point to important interactions between pia-associated microglia, pial epithelial cells, Bergman glia, and granule cells in the development of cerebellar foliation and lamination.

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**Poster**

**460. Migration During Neurogenesis**

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**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** Intramural Research Program of the National Institutes of Health, National Institute of Neurological Disorders and Stroke Grant ZIA NS002824-26

**Title:** Drebrin regulates cytoskeletal dynamics in migratory GnRH neurons through interacting with CXCR4

**Authors: *Y. SHAN**, S. WRAY
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**Abstract:** Movement of migrating neurons is regulated through rapid cytoskeletal modification (assembly/disassembly of actin filaments and microtubules) in response to guidance cues. However, the mechanism(s) by which guidance cues communicate to the cytoskeleton of migrating neurons remains unclear. GnRH neurons originate in nasal regions and migrate along olfactory sensory axons into the forebrain, where they regulate reproductive function. Numerous guidance cues ensure GnRH neurons reach their destination. Previous data indicates that: (1) stromal cell-derived factor 1 (SDF-1) via chemokine receptor type 4 (CXCR4) accelerates GnRH neuronal migration and, (2) capturing of microtubule plus ends to cortical actin in migrating GnRH neurons occurs via $Ca^{2+}$ dependent mechanisms. It is well known that during migration, cytoskeletal dynamics are regulated by cytoskeleton binding proteins. One binding protein, developmentally regulated brain protein (drebrin) has been proposed to directly interact with CXCR4 to promote actin polymerization at immune synaptic sites in T-cells and has been shown to interact with microtubule plus end binding protein EB3. Thus, drebrin is a promising candidate that may connect SDF1/CXCR4 signaling to cytoskeletal dynamics in migrating GnRH neurons. In the current study, drebrin was found to be robustly expressed along the cortical actin of migrating GnRH neurons, and was colocalized with the early expressed microtubule plus ending binding protein EB1. This expression pattern is consistent with drebrin guiding microtubule bundles into the actin cortex in migrating neurons. Confocal microscopy revealed colocalization of drebrin and CXCR4 in GnRH neurons, suggesting that communication between receptor and cytoskeletal regulator is through direct binding. Functional migration assays were performed using mouse nasal explants and pharmacological inhibition of drebrin by BTP2 (a CRAC channel blocker). Depending on the paradigm used, pre-treatment with BTP2 abrogated the effects of either CXCR4 agonists or antagonists, while not affecting migration driven via GABAARs. These data support an interaction between drebrin and CXCR4 and provide a mechanism by which guidance cues communicate to the cytoskeleton of migrating neurons.

**Disclosures: Y. Shan:** None. **S. Wray:** None.

**Poster**

**460. Migration During Neurogenesis**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 460.07/B7

**Topic:** A.01. Neurogenesis and Gliogenesis

**Title:** Neuromesodermal progenitor-neural stem cells exhibit adhesive and collective migration properties during trunk elongation

**Authors: *M. R. SHAKER**[1], J. LEE[2], W. SUN[3]
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**Abstract:** It is becoming evident that the properties of neural stem cells (NSCs) are highly heterogeneous depending on their locations and/or the developmental origin. A subset of posterior NSCs have recently shown to be derived from tail tip neuromesodermal progenitors (NMPs) which exhibit bipotential to produce either neural cells or mesodermal cells. Junctional neurulation is a unique developmental program where primary and secondary neurulation meets to shape a discrete region of the spinal cord. This transition zone of junctional neurulation is highly susceptible to neural tube defects. In vivo lineage tracing with TcreER2:Rosa-EGFP transgenic mice revealed that NMPs-NSCs born at E10 are confined to the secondary neural tube at the lumbosacral level that overlaps dorsally with primary neural tube to form the junctional neural tube. NMPs-NSCs born at E8 primarily contribute to spinal cord somatic sensory neurons. Interestingly, here we discovered that NSCs in the secondary neurulation regions is significantly adhesive and exhibit collective migration properties comparing to the NSCs in the primary neurulation region. And activation of Wnt/β-catenin signalling significantly altered primary neural tube-NSCs toward secondary neural tube-NSC-like phenotypes. These data illustrate that different adhesive properties of NSCs along with longitudinal axis of neural tubes may be implicated in the formation of junctional neurulation.

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**Poster**

**460. Migration During Neurogenesis**

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**Topic:** A.01. Neurogenesis and Gliogenesis

**Title:** Regulation of cortical principal neuron migration by KCC2

**Authors: *M. PUSKARJOV**[1], M. MAVROVIC[1], P. UVAROV[1], L. VUTSKITS[2], K. KAILA[1]
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**Abstract:** The laminar organization of the cerebral cortex comes about as result of sequential migration of neurons in an inside-out manner. Migration defects emerge as a common denominator in a number of developmental brain disorders, including seizures and autism, however the cellular and molecular mechanisms at play are poorly known. The qualitative maturation of $GABA_AR$-signaling has been proposed to act as a regulator of neuronal migration rate. The ontogenetic shift from depolarizing to hyperpolarizing GABA signaling is mediated by up-regulation of KCC2, which lowers neuronal $Cl^-$ concentration. Notably, KCC2 is a

multifunctional protein which, in addition to its role as a K-Cl cotransporter, interacts with the actin cytoskeleton in an ion transport-independent manner. Up-regulation of KCC2-mediated $Cl^-$ extrusion has been shown to regulate interneuron migration, but it is not clear whether and how KCC2 might affect principal neuron migration. Using $KCC2^{-/-}$ constitutive knockout mice we first demonstrate that global loss of this neuron-specific protein does not perturb gross cortical lamination. Then, using *in utero* electroporation of cre-recombinase in conditional $KCC2^{lox/lox}$ mice to achieve specific ablation of KCC2 in a subpopulation of migrating somatosensory principal neurons, we show that loss of KCC2 results in marked acceleration in the rate of migration of these cells. Our preliminary data suggest that this effect is rescued by co-electroporation of cre together with either wildtype KCC2 or a transport-inactive KCC2 variant that retains cytoskeletal interaction. Our data suggest a novel ion transport-independent role for KCC2 in controlling the migration rate of cortical principal neurons.

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**Poster**

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**Topic:** A.01. Neurogenesis and Gliogenesis

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**Title:** Ephrin-B expression in inhibitory neurons controls cortical excitatory-inhibitory homeostasis and seizure activity

**Authors: A. TALEBIAN**, R. BRITTON, S. AMMANUEL, J. R. GIBSON, *M. HENKEMEYER
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**Abstract: Introduction.** Excitatory-inhibitory (E/I) homeostasis is crucial for normal brain function and disruption of this balance is related to numerous psychiatric disorders associated with seizures. Several studies demonstrate the importance of EphB receptor tyrosine kinases and their transmembrane ephrin-B ligands in excitatory neurons and their synapses. However, the contribution of ephrin-B/EphB interactions in inhibitory neurons is largely unknown. Here we describe roles for ephrin-Bs in early migration of inhibitory neurons into the cortex and find how they help establishing normal populations of interneurons and E/I homeostasis in the brain. **Methods.** Using conditional triple mutants (TM) and an inhibitory neuron specific Cre driver (Dlx1/2-Cre), we selectively deleted the three ephrin-B genes and assessed seizure activity, cortical excitability, and interneuron migration and population into the cortex and hippocampus.

Our analysis was aided by a Rosa26-stop-tdTomato reporter of Cre activity and GAD65-GFP and GAD67-GFP reporters of the two main subtypes of inhibitory neurons. In addition to TM+Cre mutants, the involvement of ephrin-B reverse signaling was assessed using intracellular truncation and point mutant mice. **Results.** TM+Cre and EB2/EB3 reverse signaling mutants exhibited audiogenic seizures and increased cortical excitability as measured by electrophysiological recordings of up states. Morphological analysis demonstrated reduced migration of cortical/hippocampal interneurons in development (E13.5-E15.5) and reduced populations in adult brains. **Conclusion.** Our data indicate inhibitory neuron expressed ephrin-B proteins and their interactions with EphB receptors are critical for normal tangential migration of interneurons in the developing brain. They further show that loss of these molecules affects E/I homeostasis and leads to cortical hyperexcitability.

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**Poster**

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**Title:** Dual origin of enteric neurons in vagal schwann cell precursors and the sympathetic neural crest

**Authors: *I. ESPINOSA MEDINA**[1,2], B. JEVANS[3], F. BOISMOREAU[2], Z. CHETTOU[2], H. ENOMOTO[4], T. MÜLLER[5], C. BIRCHMEIER[5], A. J. BURNS[3], J.-F. BRUNET[2]
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**Abstract:** Neural crest cells migrate extensively to form the autonomic nervous system including sympathetic, parasympathetic and enteric ganglia essential for regulating bodily homeostasis. Our previous work demonstrated that parasympathetic ganglia derive from Schwann cell

precursors (SCPs) and migrate along their preganglionic nerves to locate close to their target tissues (Espinosa-Medina et al., 2014). SCPs were previously known to give rise to melanocytes, endoneurial fibroblasts and dental mesenchymal cells as well as Schwann cells in vivo, and our study extends their fate to neurons. More recent evidences suggested that enteric ganglia, which innervate the gastrointestinal tract, might also derive from SCPs and my present work focuses on this subject. Most of the enteric nervous system is known to derive from the neural crest that lies at the level of somites 1 to 7, classically designated as the "vagal crest". These crest cells invade the digestive tract in a rostro-caudal wave of migration from the foregut to the hindgut in ways that have been extensively studied. In contrast, remarkably little is known about the initial phase of this colonization, that brings enteric precursors into the foregut, i.e. the esophagus and stomach. Here we show that the so-called "vagal crest" subsumes two populations of enteric precursors with contrasted origins, initial paths and modes of migration, and final destinations. Neural crest cells adjacent to somites 1 and 2 produce SCPs that colonize the esophagus and stomach, guided by the vagus nerve. Neural crest cells adjacent to somites 3 to 7 belong to the sympathetic crest: they enter a ventral pathway, seed the sympathetic chain, overshoot the aortas and colonize the entire digestive tract thence. Accordingly, enteric ganglia, like sympathetic ones, depend on signaling by Neuregulin-1 through the tyrosine kinase receptor ErbB3, while half of the esophageal ganglia, like parasympathetic ones, require the nerve-associated form of Neuregulin-1. The implication of the ErbB3 signaling system in the prenatal development of the enteric nervous system might bear relevance to Hirschprung disease, with which alleles of Neuregulin 1 were found associated.

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**Poster**

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**Title:** Effects of alcohol abuse on proliferating cells, neural stem cells and immature cells in the adult human hippocampus

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**Abstract:** In animal studies, impaired adult hippocampal neurogenesis is associated with behavioral pathologies including addiction to alcohol. We hypothesize that alcohol abuse may have a detrimental effect on the neurogenic pool of the dentate gyrus in the human hippocampus. In this study we investigate whether alcohol abuse affects the number of proliferating cells, neural stem cells and immature neurons in samples from postmortem human hippocampus. The specimens were isolated from deceased donors with an on-going alcohol abuse, and from controls with no alcohol overconsumption. Mid-hippocampal sections were immunostained for Ki67, a marker for cell proliferation, Sox2, a neural stem cell marker and DCX, a marker for immature neurons. Immunoreactivity was counted in alcoholic subjects and compared to controls. Counting was performed in the three layers of dentate gyrus; the subgranular zone, the granular cell layer and the molecular layer. Our data showed reduced numbers of proliferating cells, neural stem cells and immature neurons in the dentate gyrus. This reduction was most prominent in the subgranular zone, and uniformly distributed across the distances from the granule cell layer. Further, alcohol abusers showed a more pronounced reduction of Sox2 positive cells than DCX positive cells, suggesting that alcohol primarily causes a depletion of the neural stem cell pool and that immature neurons are secondarily affected.
These results are in agreement with observations of impaired adult hippocampal neurogenesis in animal studies and lend further support for the association between hippocampal dysfunction and alcohol abuse.

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**Poster**

**460. Migration During Neurogenesis**

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**Program#/Poster#:** 460.12/B12

**Topic:** A.01. Neurogenesis and Gliogenesis

**Title:** The role of Camdi during GnRH cell migration

**Authors: *H. CHO**
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**Abstract:** In the developing nervous system, newly born neurons must correctly migrate from their place of origin to their final location to form proper neural circuits. Failure of neurons to properly self-assemble into functional circuits is thought to underlie a number of neurological disorders. To study molecular mechanisms controlling neuronal migration, the linkage between failure of gonadotropin-releasing hormone (GnRH) cell migration and a specific phenotype of Kallmann syndrome provides a model system with unique attributes to unravel steps controlling neuronal migration. Recently, we reported a novel mutation (p.R724X) in the *CCDC141* gene in Kallmann syndrome patients that also have a partial loss of function mutation in *FEZF1*. Since the *FEZF1* mutation showed 50% activity, we wondered whether the mutation in *CCDC141* was also involved in the phenotype. To study *CCDC141* in GnRH cell migration, Ccdc141 expression in mouse embryos was examined. We showed that 1) Ccdc141 was expressed in migrating GnRH neurons and that 2) knockdown of Ccdc141 using siRNA reduced GnRH neuronal migration but not olfactory axon outgrowth. To further investigate the role of Ccdc141 *in vivo*, we obtained *Ccdc141* KO mice and are analyzing the number of GnRH cells in the brain. Preliminary data indicate that *Ccdc141* KOs have only ~50% of GnRH cells as compared with WT mice. Further time points are being examined to determine the impact of loss of Ccdc141on GnRH cell migration and survival during development. Our new data from KO mice are consistent with Ccdc141 playing a role in GnRH cell migration. We are currently characterizing the effect of Ccdc141 on cytoskeletal dynamics and/or calcium flux in GnRH cells during the cell migration. This study will provide new insight regarding the role of Ccdc141 involved in neuronal cell migration and pathogenic mechanism of Kallmann syndrome.

**Disclosures: H. Cho:** None.

**Poster**

**460. Migration During Neurogenesis**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 460.13/B13

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** CIHR

**Title:** Impact of energy consumption and autophagy on neuronal migration

**Authors: *C. BRESSAN**[1,2], M. SNAPYAN[1,2], S. LABRECQUE[1,2], J. KLAUS[3], D. GAGNON[1,2], M. PARENT[1,2], P. DE KONINCK[1,2], S. P. ROBERTSON[4], S. CAPPELLO[3], A. SAGHATELYAN[1,2]
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**Abstract:** Cell migration is a dynamic, ATP dependent process, essential for brain development. The dynamic morphological remodeling of migrating cells leads to the formation of protein aggregates, organelle damage and plasma membrane leftovers. One of the intracellular catabolic pathways that maintain cellular homeostasis is autophagy. Here we evaluated the involvement of autophagy and its link to energy level in neuronal migration. We used rostral migratory stream of adult mice as a model and found that autophagy-related proteins are present in 60% of neuroblasts. Time-lapse imaging of autophagosomes labeled with GFP-RFP-LC3 shows an active autophagic flux with an increase in the density of autophagosomes during stationary phases. Pharmacological alteration of cell migration led to the changes in autophagy, by increasing the level of LC3 lipidated form (LC3-II) which is specifically associated with autophagosomes. This was accompanied by changes in the expression of focal adhesion (FA) molecules. On the other hand, genetic impairment of autophagy in neuroblasts either using inducible Atg5 KO mice or by CRISPR/Cas9 technology targeting ULK1 and ULK2 decreased the distance of cell migration because of an increase in the percentage of stationary periods. The same deficit is observed when AMPK, an energy sensor and autophagy activator, is blocked by CompoundC, hinting a role of energy levels in autophagy activation. Energy monitoring by live imaging in neuroblasts, using PercevalHR, a ratiometric sensor of ATP/ADP, shows a decrease of energy during migratory phases and an increase during stationary periods. This result, correlated with an increase in autophagosomes during stationary periods, reinforces the link between energy and autophagy. We next asked if the level of autophagy is also altered in some neurodevelopmental disorders resulting from affected neuronal migration. Individuals suffering from a form of neuronal periventricular heterotopias have mutations in genes encoding cadherin ligand (Dchs1) and receptor (Fat4). We first determined the expression of autophagy-related proteins in human organoids derived from neural progenitor cells (NPC) of healthy individuals and subjects with mutated Fat4 and Dchs1 genes. We observed a striking change in the LC3-II as well as in the expression of FA molecules. Graft of human NPC into mouse postnatal neurogenic regions also revealed alterations in cell migration of cells derived from subjects with Fat4 and Dchs1 mutations. Altogether, we show that autophagy may be activated because of energetic needs and is required for cell migration under normal and pathological conditions.

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**Poster**

**460. Migration During Neurogenesis**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 460.14/B14

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** Israel Science Foundation

The Open University Research Fund in Israel

Council for Higher Education in Israel

**Title:** New neuronal migration: Spatial distribution in the Nidopallium Caudale (NC) of the adult avian brain

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**Abstract:** This study engages with the process of neurogenesis in adult birds, in which new neurons are born in the ventricular zone, and then migrate over long distances to other brain regions. We investigated the patterns of such migration process of the new neurons in brains of male zebra finches *(Taeniopygia guttata*) using BrdU treatment and recording, quantitatively and spatially, their distribution neurons in the Nidopallium Caudale (NC) at several time points after their birth: 7, 21, 35, and 42 days.
In birds, the NC is a brain region in the telencephalon that consists of three sub-regions: **Nidopallium caudalomediale** (NCM) - is important for song perception and discrimination, storage of auditory memories, and is analogous to supragranular layers of the auditory cortex of mammals. **Nidopallium caudolaterale** (NCL) - is an associative region that is important for cognition, and has a role in working memory, decision-making behaviors (including those required for judgments of numerical ability, reversal learning, and reward prediction), and is considered functionally equivalent to the prefrontal cortex in mammals. **Nidopallium caudocentral** (NCC) - is involved in neuroendocrine and autonomic functions and is limbic in nature.
Overall, density of new neurons in the NC did not show age-dependence changes, but varied significantly between its sub-regions. A higher percentage of new neurons occurred in the NCM, compared with the two other sub regions (NCC and NCL), at all the time points, even though NCM is the smallest sub-region. In addition, NCC and NCL exhibited similar levels of neuronal recruitment. This non-random spatial distribution of new neurons in the NC suggests that its sub-regions differ in their amount of plasticity. The greater plasticity of NCM might further imply that song perception and discrimination in male zebra finches require higher rates of neuronal turnover, compared with the functions that are processed in the two other sub-regions. This differential neuronal plasticity within the NC supports the previously suggested division of this large brain region, which is based on connectivity patterns, dopaminergic innervations, and induction of ZENK.

**Disclosures:** **M.A. Atamna:** None. **A. Hefetz:** None. **A. Barnea:** None.

**Poster**

**460. Migration During Neurogenesis**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 460.15/B15

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** NINDS R01 NS066071 to E.C.O.

NIH R01 CA163296 and R01 GM047607 to C.E.T.

**Title:** Conditional knockout of paxillin disrupts the morphology and speed of migrating neurons and is associated with delayed cortical layer formation

**Authors: *M. RASHID**[1], J. BELMONT[1], D. CARPENTER[1], C. TURNER[2], E. OLSON[3]
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**Abstract:** Paxillin, Hic-5 and leupaxin are homologous focal adhesion adaptor proteins that coordinate cytoskeletal rearrangements in response to integrin-signaling and changing extracellular environments. Leupaxin is not expressed in the brain cortex while Hic-5 null mice have no described cortical phenotype and paxillin null mice die prior to brain development. Thus, the function of this family of proteins during cortical development is unknown. Here, we find that Hic-5 deficient mice are postnatal viable with normal cortical layering. Mice with a neural-specific deletion of paxillin (*Nes-Cre:Pxn$^{F/F}$*) are also postnatal viable, but show evidence of a cortical neuron migration delay that is evident pre and perinatally, but is not detected at postnatal day 35 (P35). This phenotype is not modified by Hic-5 deficiency (double knockout). Specific deletion of paxillin in postmitotic neurons (*NEX-Cre:Pxn$^{F/F}$*) also causes the migration delay, suggesting a requirement for paxillin in actively migrating neurons. *In utero* electroporation of a Cre-expression construct into *Pxn$^{F/F}$* embryonic cortex identified a cell-autonomous requirement paxillin and revealed that paxillin-deficient migrating neurons have significantly shorter leading processes that exhibited multiple swellings in comparison to control. Multiphoton imaging of cortical explants reveals that paxillin-deficient neurons migrate 30% slower than control neurons. This morphological phenotype is similar to the reported phenotype produced by conditional deletion of focal adhesion kinase (FAK), a critical signaling partner of paxillin and suggests that paxillin functions with FAK in a cell-autonomous manner, to control the morphology and speed of migrating neurons during cortical development.

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**Poster**

**460. Migration During Neurogenesis**

**Location:** Halls A-C

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**Program#/Poster#:** 460.16/B16

**Topic:** A.01. Neurogenesis and Gliogenesis

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**Title:** Alternative splicing of Disabled-1 controls multipolar-to-bipolar transition of migrating neurons in the neocortex

**Authors: *B. ZH**[1], W. WANG[1], Z. ZHANG[1], Y. HU[1], F. MENG[1], F. WANG[1], H. LOU[1], L. ZHU[1], R. GODBOUT[2], S. DUAN[1], Z. GAO[1]
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**Abstract:** How neurons undergo multipolar-to-bipolar transition (MBT) in the upper intermediate zone (IZ) to migrate radially towards the cortical plate remains unclear. Reelin-induced tyrosine phosphorylation of Disabled-1 is essential for radial migration. We have previously shown that alternative splicing produces multiple Dab1 isoforms with different tyrosine motifs and differential ability to recruit downstream effectors. Here we report that splicing of exons 7&8 and 9bc occurs in a mutually-exclusive fashion in the IZ of the neocortex, dynamically regulating the inclusion and activities of Dab1 tyrosine motifs. Our *in utero* electroporation studies show that expression of Dab1 isoforms missing exons 7&8 or retaining exons 9bc in WT neurons delayed cortical neuronal migration with attenuated Dab1 tyrosine phosphorylation, and disrupted leading process extension and orientation of multipolar neurons in the multipolar accumulation zone (MAZ). Introducing the canonical Dab1 form, but not those missing exons 7&8 or retaining exons 9bc, into Dab1-deficient neurons promoted MBT and rescued neuronal migration defects, suggesting that alternative splicing of Dab1 modulates the tyrosine motif switch and mediates MBT of cortical neurons. Our study reveals a critical mechanism for coordinated control of Reelin-mediated neuronal migration at both pre- and post-translational levels.

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**Poster**

**460. Migration During Neurogenesis**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 460.17/B17

**Topic:** A.01. Neurogenesis and Gliogenesis

**Title:** Isolating deterministic, stochastic and directional persistence elements of migrating neurons: time-lapse analysis of in-vitro cultures of GABAergic and glutamatergic cortical neurons

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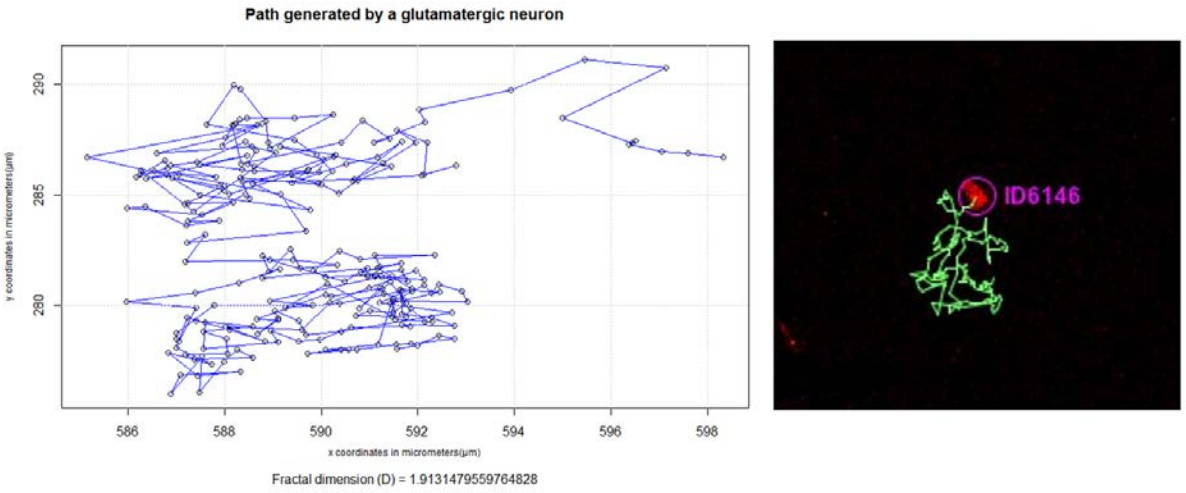
**Abstract:** Migrating cortical neurons move through long, highly stereotypical paths until they reach their targets by detecting cues in the environment, thought to be gradients in the concentration of various neurotrophic factors. However, observed paths are rarely smooth curves, indicating that guidance is not fully deterministic. Understanding the stochastic events that underlie these migration patterns could lead to new insights for the study of development and connectivity of the cortex, and may help how migration occurs (or fails to occur) in the presence of intermittent and/or noisy cues. To that end, we conducted long time-lapse analysis of cortical GABAergic interneurons and projection glutamatergic neurons as the neurons navigated, either freely in a cell-dissociated milieu or in cue-oriented spaces in cell-culture dishes. Migration patterns were then extracted algorithmically and analyzed. For both types of neuron, with or without cues, we calculate the fractal dimension of the tracks, to determine their stochastic component, which was modelled as a random walk. We further measure track characteristic persistence length and correlation function, and the deterministic response to constant-gradient cues. We use this data to test a stochastic model that regards neuronal migration as the additive combination of these three effects , and look for evidence of interaction effects. We seek to further characterize the response to cue by isolating the deterministic response to varying-gradient cues.




**Disclosures:** **E.S. Morsch:** None. **D. Rayêe:** None. **M. Lourenço:** None. **B. Mota:** None. **P. Garcez:** None.

**Poster**

**460. Migration During Neurogenesis**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 460.18/B18

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** Jim and Betty Ann Rodgers Chair Fund

**Title:** Developmental nicotine exposure and GABA neuron development

**Authors: *M. M. MARTIN**[1], D. M. MCCARTHY[2], P. G. BHIDE[2]
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**Abstract:** Cigarette smoking during pregnancy is a major public health concern because it can have detrimental effects on both the mother and her child. For example, developmental nicotine exposure (DNE) is associated with increased risk for ADHD, conduct disorder, learning disabilities, anxiety, epilepsy, and depression. The GABA neurotransmitter system is known to be altered in many of these developmental disorders raising the possibility that DNE may target the GABA system in the developing brain. During embryonic development, the majority of the GABA neurons originate in the medial ganglionic eminence of the basal forebrain and migrate tangentially to regions of the dorsal forebrain. Here we examined the effects of DNE on the GABAergic system during the embryonic period using a GAD67-GFP knock-in mouse model. In this model, GABA neurons are GFP+, facilitating their identification. Female mice were exposed

to plain drinking water or water containing nicotine (100 or 200 µg/ml) beginning 3 weeks prior to conception and throughout pregnancy. We found that DNE produces a significant increase in the number of GABA neurons in the intermediate and marginal zones of the dorsal forebrain in 15-day old embryos in both the nicotine groups, suggesting that DNE alters the GABA neuron migration from the basal to the dorsal forebrain. Since perturbation of developmental pathways can lead to lasting changes in the mature brain, ongoing studies are examining the effects of DNE on the number and location of GABA neurons in the mature brain.

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**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

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**Program#/Poster#:** 461.01/B19

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** JSPS KAKENHI 16H01329

JSPS KAKENHI 17H03988

JSPS KAKENHI 17H05738

**Title:** Differentiation of human induced pluripotent stem cell (hiPSC)-derived neurons in mouse hippocampal slice cultures

**Authors: *T. HIRAGI**[1], M. ANDOH[1], T. ARAKI[2], T. SHIRAKAWA[3], T. ONO[2], R. KOYAMA[1], Y. IKEGAYA[1]
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**Abstract:** Potential clinical applications of neurons derived from human induced pluripotent stem cells (hiPSC-neurons) for drug screening and transplantation therapies have received considerable attention. However, it remains unclear whether and how transplanted hiPSC-neurons are incorporated into pre-existing neural circuits. Here we developed a co-culture system of hiPSC-neurons and mouse hippocampal slices to examine the differentiation of hiPSC-neurons in pre-existing neural circuits. hiPSC-neurons that were transplanted in the neuronal cell layers of hippocampal slice cultures expressed the hippocampal neuron-specific markers HuB and Prox1 after 7 days of culture. In contrast, hiPSC-neurons that were transplanted outside the neuronal cell layers often expressed the astrocytic marker GFAP. Furthermore, hiPSC-neurons in the dentate granule cell layer grew to exhibit dentate granule cell-like morphologies, including besom-shaped dendrites. Similarly, hiPSC-neurons in the CA1 pyramidal cell layer grew to

exhibit CA1 pyramidal cell-like morphologies, including primary apical and multiple basal dendrites with synaptic spines. Additionally, hiPSC-neurons in the CA1 pyramidal cell layer projected axons toward the entorhinal cortex as observed *in vivo*. These data suggest that hiPSC-neurons were anatomically integrated into pre-existing neural circuits in a region-specific manner. Thus, the co-culture system will be useful for the study of efficient strategies to differentiate transplanted hiPSC-neurons in recipients.

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**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.02/B20

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Motor neurons derived from human embryonic stem cells- a human cell model for amyotrophic lateral sclerosis

**Authors: *T. R. RAJU**[1], R. SUMITHA[2], V. M. MANJUNATHA[3], K. SABITHA[4], P. A. ALLADI[4], A. NALINI[5], R. T. LAXMI[4], C. B. K. SAGAR[6], B. W. KRAMER[7], T. SATHYAPRABHA[4]
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**Abstract:** Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease caused by the loss of both upper and lower motor neurons (MNs) leading to paralysis of the voluntary muscles with death ensuing within 2-5 years of clinical onset due to respiratory failure. Most of the research on ALS encompasses the use of transgenic SOD1-familial model and the sporadic rat models (both *in-vivo* and *in-vitro*) derived using Cerebrospinal Fluid (CSF) from ALS patients. Although animal models aid in understanding the pathogenesis and disease progression to a considerable extent, they may not faithfully reproduce the human syndrome due to species differences. Hence, there is a critical need for the use of cells from human source to understand the disease pathogenesis and overcome the pit falls associated with poor correlation between the animal models and the human disease .In this study, we have attempted to establish a pre-clinical model, which involves determining the response of human Embryonic Stem Cells (hESCs) derived spinal MNs to CSF from sporadic ALS patients. hESCs (BJNHem20) were maintained on inactivated mouse embryonic fibroblasts and differntiated into motor neurons using retinoic acid and purmorphamine. They were characterized using RT-PCR, immunostaining and flow

cytometry. Differentiated cells were positive for a panel of MN specific markers HB9, Islet1, FOXP1 and Choline Acetyl Transferase. At the ultra-structural level, hESC derived MNs showed loosely spread Nissl substances, neurofilaments and the neuronal processes carrying mitochondria characteristic of neurons. Extracellular recordings were performed from MNs at different days of maturation using Multi Electrode Array. MNs generated spontaneous action potentials at Day23 and fired with <5 Hz and >5 Hz frequencies characteristic of principal and putative interneurons respectively. The principal neurons fired more number of spikes on Day33 of maturation compared to other days. MNs at Day33 were exposed to ALS-CSF and the following changes were observed: altered expression of neurotrophic factors and cytoskeletal proteins; organelle dysmorphology at the ultra-structural level; reduced activity of mitochondrial respiratory chain complexes; trend of decrease in BCL2/Bax ratio and up-regulated expression of Caspase 9. With the wealth of data already built around animal/ cell culture model of sporadic ALS in our laboratory, our humanized model was able to reproduce multiple factors involved in the pathogenesis of ALS validating the utility of this model for future studies.

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**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.03/B21

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Stemdiff cerebral organoid kit: A new tool for the culture of 3-D brain organoids derived from human pluripotent stem cells

**Authors: *V. M. LEE**[1], L. H. CHEW[1], A. AÑONUEVO[1], S. LLOYD-BURTON[1], A. C. EAVES[1,2], T. E. THOMAS[1], S. A. LOUIS[1]
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**Abstract:** 2-D neural cultures derived from human pluripotent stem cells (hPSCs), including human embryonic and induced pluripotent stem cells (hESCs or hiPSCs), are useful models with which to study the nervous system, but they are limited in their capacity to fully recapitulate the complex organization of brain tissues. Lancaster et al. (Nature 2013) established a hPSC-based organoid culture system that models the major features of early human brain development. Based on the published media formulations, we developed the STEMdiff™ Cerebral Organoid Kit to enable generation of organoids in a simple and highly reproducible manner. This kit contains 2 basal media and 5 supplements, which are combined to prepare four separate complete media

corresponding to the 4 stages of cerebral organoid formation. hPSCs maintained in mTeSR1™ were single-cell dissociated and cultured in Embryoid Body (EB) Formation Medium in U-Bottom plates (day 1 - 5, Stage 1). The resulting EBs were then transferred to Induction Medium (day 6 - 7, Stage 2); next, they were expanded by embedding in Corning® Matrigel® and cultured in Expansion Medium (day 7 - 10, Stage 3). The expanded organoids were then cultured in Maturation Medium, with agitation, for extended periods of time (day 10 - 40+, Stage 4). Morphological analysis of organoids was performed on days 5, 7, 10 and 40, which are the endpoints of Stages 1 - 4 respectively. Organoids at Day 40 were analyzed by RT-qPCR or cryosectioned and processed for immunofluorescence (>3 organoids per analysis; 2 hESCs, n = 2 and 2 iPSCs, n = 2). We achieved high efficiencies across multiple cell lines (2 hESCs, n = 2 and 2 iPSCs, n = 2) for EB generation (100% success, n = 128/128), expansion (>95% exhibited extensive folding of neuroepithelia, n = 104/107) and maturation (>60% of organoids were >1 mm in diameter with dense cores , n = 62/94). These outcomes are a significant improvement upon the published protocol and reagents, with which <30% of the generated organoids had the desired morphology. In vivo, the human cortex consists of progenitor and neuronal populations that organize into distinct layers. The mature organoids generated here exhibited a similar architecture with neural progenitors (SOX2+, PAX6+) localized in apical regions surrounding a central ventricle. Adjacent to the apical progenitors, neuronal progenitors (TBR2+, Ki-67+) were found abutting neurons (CTIP2+, MAP2+, TBR1+), resembling the intermediate zone and cortical plate regions. Taken together, our data demonstrate that the STEMdiff™ Cerebral Organoid Kit supports highly efficient generation and expansion of cerebral organoids, and improves upon currently available methods.

**Disclosures:** **V.M. Lee:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **L.H. Chew:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **A. Añonuevo:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **S. Lloyd-Burton:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc.. **A.C. Eaves:** None. **T.E. Thomas:** A. Employment/Salary (full or part-time):; STEMCELL Technologies. **S.A. Louis:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc..

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.04/B22

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Characterization of Caudal Cell Mass (CCM): A key to understanding secondary neurulation in chick embryo

**Authors: *V. KIM**[1], A. ZAIDI[1], S. KIM[1], K. WANG[3], J. LEE[2,3]
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**Abstract:** Background>
The Caudal Cell Mass (CCM) is an aggregated mass of progenitor cells situated near the tail bud. In the chick embryo, it has been previously confirmed that the CCM ultimately gives rise to the secondary neural tube and therefore is well involved in secondary neurulation. It is necessary to gain a better understanding of the identity of progenitor cells in the caudal cell mass active during secondary neurulation and their molecular background in both spatial and temporal manner. Characterization of this region will provide future implications for solving the limited knowledge on the mechanisms at fault during the failure of neural tube closure, which are ultimately responsible for Neural Tube Defects, the most common birth defect in newborns to current date. However, the cellular identity of the CCM is not well known.
Materials and Methods>
We have used a carefully selected set of mesenchymal and neural markers to identify the temporal characteristics of the CCM throughout embryonic development in chicks. As mesenchymal markers, Brachyury T, CD44, CD29 were closely examined. Neural markers were listed as Sox2, Nkx1.2, and N-cadherin. The RNA expression level and protein level were analyzed using qPCR and immunohistochemistry. Different stages during development of chick embryo (Hamburger and Hamilton stage from 12 to 35) were examined. By analyzing the trend of marker expression, we were able to illustrate the progenitors present at specific stages and how their expression levels change throughout development.
Results>
The immunohistochemistry results show most prominent staining at the earlier stages by the mesenchymal markers, especially However, the stage for the most high expression did not correlated as much.Results suggest that the CCM maintains mesenchymal character at an early stage, and this decreases through development. Neural character on the other hand seems to maintain presence throughout.
Conclusion>
Our findings suggest that the caudal cell mass starts out as an aggregated mass of neuromesenchymal progenitor (NMP) cells with strong expression of both neural and mesenchymal characters, and with development it maintains neural character but gradually loses the mesenchymal character.

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**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.05/B23

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** Rainwater Charitable Foundation

StemCultures

**Title:** More efficient differentiation of iPSC derived neurons with controlled release of BDNF

**Authors: D. C. BUTLER**[1], S. LOTZ[1,2], S. K. GODERIE[1], E. H. STANTON[1], N. S. Z. KOTB[1], *A. MESSER[1], S. TEMPLE[1,2]
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**Abstract:** Induced pluripotent stem cell (iPSC) derived neurons are valuable for disease modeling and drug screening. Several protocols have been developed for forebrain cortical differentiation. Many neuronal differentiation protocols deliver soluble brain derived neurotrophic factor (BDNF) and/or glial cell-derived neurotrophic factor (GDNF) to support neuronal production and survival. These require refeeding every other day. This bolus delivery system imperfectly models the more stable in vivo environment: with excess levels of growth factor protein immediately after refeeding, followed by lowering levels due to growth factor instability down to suboptimal prior to the next feed. Furthermore, this process is labor intensive, and wastes valuable neurotrophic factor protein. PLGA microspheres (StemBead®) have previously been shown to control the release of fibroblast growth factor 2 (FGF2) for the maintenance of iPSCs. The goal of the current study was to determine if controlled release of growth factors with PLGA microspheres could deliver BDNF and GDNF in a more stable and effective manner.
Growth factor microspheres were optimized for size and levels of released protein. A size range of 10-20μm produced sustained growth factor levels in culture medium for 6+ days, measured both biochemically and functionally. To generate forebrain cortical neurons, iPSCs were first differentiated into neural precursor cells (NPCs) by forming embryoid bodies in neural induction media with dual SMAD inhibition on poly-L-Ornithine-Laminin substrate. Pax6, Nestin, and Sox2 -positive NPCs were differentiated using N2/B27, DMEM/F12, Neurobasal base media supplemented with either soluble factor every 2-day feeding or StemBeads® growth factor delivery with every 4-day feeding. In our 30-day protocol, stabilization of BDNF protein levels using controlled release PLGA microspheres improves the neurite outgrowth and branching of MAP2 positive iPSC derived neurons when compared to soluble growth factor delivery. Preliminary data suggest GDNF responses are similarly improved with controlled release. Parallel studies using iPSCs from neurodegenerative disease individuals are in progress. In summary, controlled release of BDNF and GDNF using PLGA StemBeads® reduces time, cost, and effort, while generating more complex human iPSC derived neurons for use in disease phenotyping and therapeutic testing.

**Disclosures: D.C. Butler:** None. **S. Lotz:** None. **S.K. Goderie:** None. **E.H. Stanton:** None. **N.S.Z. Kotb:** None. **A. Messer:** None. **S. Temple:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.06/B24

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIGMS GM109089

**Title:** Default patterning of human pluripotent stem cells results in pan-cortical and CGE/LGE-like subpallial specification

**Authors: *C. FLORUTA**[1], M. FISCHER[2], R. DU[3], H. KANG[4], J. L. STEIN[5], J. P. WEICK[2]
[1]Neurosci., [2]Neurosciences, [3]UNM Comprehensive Cancer Ctr., [4]Dept. of Intrnl. Med., Univ. of New Mexico, Albuquerque, NM; [5]Dept. of Genet. & UNC Neurosci. Ctr., Univ. of North Carolina Sch. of Med., Chapel Hill, NC

**Abstract:** Previous studies have reported that human pluripotent stem cells (hPSCs) generate dorsal forebrain, cortical-like neurons under default differentiation in the absence of patterning morphogens. While a preponderance of neurons do express cortical layer markers and are glutamatergic, their regional specification remains unclear. Furthermore, a significant population of GABAergic neurons also develop under non-directed conditions. To gain insight into the diversity of neuronal populations generated by default patterning we first performed bioinformatic analyses using Transition Mapping (TMAP), CoNTExT, and WGCNA on developmental transcriptome data to allow us to examine the overall regional and temporal specification compared to *in vivo* human brain samples. Temporally, we found that day 50 hPSNs resembled mid-gestational fetal brains, and displayed a panoply of functional markers of synaptic transmission. In addition, gene expression profiles of default differentiated hPSNs represent a pan-cortical identity with expression of markers that are differentially expressed across rodent cortex. Spatially, our analyses revealed significant overlap with multiple layers of developing human pallium. However, we also identified a robust subpallial transcriptional profile, as evinced by the presence of markers for GABAergic progenitors and post-mitotic neurons including *DLX1/2/5/6, ASCL1, GAD1, SST, NPY, CALB2*, and multiple GABA receptor subunits. Interestingly, using qPCR, the preponderance of expressed subpallial markers showed significant overlap with genes expressed in CGE/LGE domains (e.g. *NR2F2, MEIS2, FOXP4, PBX1*), but not MGE domains (e.g. *NKX2-1, GBX1/2, LHX6*). CGE identity was further confirmed by increased COUPTFII and Calretinin (CALB2) staining in GABA-positive cells. Interestingly, WNT inhibition following neural induction caused hPSNs to adopt a significantly more dorsal regionalization, with a higher correlation between *in vivo* cortex and significant reductions in GABAergic neuronal gene expression. Taken together, our data point to a WNT-dependent patterning of LGE/CGE-like GABAergic neurons from default-patterned cells, and

provide a more comprehensive understanding of the signaling event leading to the diverse population of hPSNs generated by default patterning.

**Disclosures: C. Floruta:** None. **M. Fischer:** None. **R. Du:** None. **H. Kang:** None. **J.L. Stein:** None. **J.P. Weick:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.07/B25

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NSERC discovery grant 2NS

CFI 2NS

CRC 2NS

**Title:** Augmented stem cell potential in response to environmental enrichment is seen in juveniles but not adults

**Authors: *K. CHANDLER**[1], H. DOSSO[1], N. SALMASO[1,2]
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**Abstract:** Early in telencephalic development, neural stem cells are born in the ventricular zone and migrate through the cortex before differentiating into neurons and glia. Adult neurogenesis, however, is limited to specific niches in the brain: the dentate gyrus of the hippocampus (DG) and the subventricular zone (SVZ). The proliferation and differentiation potential of these neural stem cells is plastic and shows changes across states and in response to environmental manipulations. It has previously been shown that short-term environmental enrichment (Enr) is sufficient to increase the proliferation and differentiation of the GFAP+ stem cell pool in juvenile mice. Because longer-term Enr protocols are typically used to induce behavioural and functional recovery in adult mice, it is expected that that short-term Enr will be sufficient to induce an increase in neural stem cell potential only in juveniles. Using male C57 wildtype mice, we examined the potential of SVZ and DG NSCs in vitro following short-term Enr using neurosphere assays in both juvenile (P35) and adult (P90) mice. The assays were examined for NS number, size, and differentiation potential. We also examined changes in cognitive and anxiety behaviour. As hypothesized, we found that the short-term Enr increased learning and memory in juvenile mice, but not in the adult mice. These changes paralleled increased proliferation and differentiation of the stem cell pool in juveniles that was less pronounced in

adults, suggesting developmental decreases in NSC potential in response to short-term environmental manipulations.

**Disclosures: K. Chandler:** None. **H. Dosso:** None. **N. Salmaso:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

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**Program#/Poster#:** 461.08/B26

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIH Grant EY024984

Indiana Department of Health

**Title:** Retinal organoids derived from human pluripotent stem cells exhibit a defined ganglion cell layer and allow for the modeling of glaucomatous autophagy deficits and neurodegeneration

**Authors: *K. LANGER**[1], A. SRIDHAR[2], H. TSENG[3], J. S. MEYER[1]
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**Abstract:** Retinal organoids are three-dimensional structures derived from human pluripotent stem cells (hPSCs) mimicking both the temporal the spatial organization of the native retina. The ability to derive retinal cells in such a way allows for a model closely resembling the spatiotemporal development of the human retina. Furthermore, retinal cells derived in this manner would be more likely to exhibit a full complement of features associated with bona fide retinal neurons. Although numerous studies have demonstrated the development and functionality of photoreceptors in retinal organoids, the development of retinal ganglion cells (RGCs) within organoids has been mostly overlooked. RGCs provide the vital pathway between the eye and the brain, allowing for the ability to see. In neurodegenerative diseases of the eye, such as glaucoma, this vital connection is damaged, resulting in loss of vision and blindness. As the mechanisms by which this degeneration occurs remain unclear and few therapeutic options are available, the development of retinal organoids represents an exciting and novel approach for the study of RGC development and disease. Thus, efforts were focused on the generation of RGCs within inner layers of retinal organoids with this differentiation occurring through identifiable stages closely resembling retinogenesis. Furthermore, the ability for retinal organoids to serve as an effective model for glaucomatous degeneration of RGCs was investigated by using hPSCs derived from a glaucoma patient with the E50K mutation in the Optineruin gene. RGCs derived in this fashion exhibited autophagy deficits such as the accumulation of LC3 aggregrates, as well as increased activation of apoptotic markers within the RGC layers of the organoid.

Treatment of patient-derived RGCs with autophagy activators was further performed to determine the link between autophagy disruption and apoptotic cell death. Thus, the results of study represent the first efforts to utilize retinal organoids to effectively model the development of RGCs within organoid structures, as well as serve as a novel approach for the modeling of glaucomatous neurodegeneration.

**Disclosures:** **K. Langer:** None. **A. Sridhar:** None. **H. Tseng:** None. **J.S. Meyer:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

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**Program#/Poster#:** 461.09/B27

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** FONDECYT Nº1150933

**Title:** Wnt5a regulates proliferation and differentiation of adult neural progenitor cells and morphological development of the derived neurons

**Authors: S. B. ARREDONDO**, F. GUERRERO, J. JENSEN-FLORES, D. B. BUSTAMANTE, *L. VARELA-NALLAR
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**Abstract:** Wnt ligands comprise a family of glycoproteins that participate in cell-cell communication and regulate diverse processes during development including stem cell-renewal and differentiation. In the brain, the Wnt signaling is implicated in dendrite development, synapse formation and synaptic plasticity. Specifically, the Wnt5a ligand that is expressed in hippocampal neurons, is essential for dendritic spine morphogenesis and dendrite maintenance. Here, we evaluated the role of Wnt5a in cell-renewal and differentiation of adult neural progenitor cells (aNPCs) isolated from the hippocampus of 6-week-old mice. Proliferating aNPCs were maintained in serum free media supplemented with EGF and FGF-2. Proliferation was measured by BrdU incorporation. Differentiation was induced by growth factors withdrawal. Neuronal and astrocytic differentiation was evaluated using specific markers. We determined that treatment with Wnt5a, as well as Wnt3a used as control, increased proliferation of aNPCs. After growth factors withdrawal only Wnt5a induced neuronal differentiation without affecting differentiation into astrocytes. In agreement, Wnt5a-knockdown in aNPCs by lentivirus-mediated shRNA reduced neuronal differentiation not affecting astrocytic differentiation. Finally, we evaluated morphological development of aNPCs-derived neurons, which show a significant increase in dendritic complexity 2, 4 and 6 days after induction of differentiation. Wnt5a-knockdown reduced dendritic arborization of aNPC-derived neurons compared to neurons expressing control shRNA. Our data indicate that Wnt5a stimulates self-renewal of

proliferating aNPCs, and induces neuronal differentiation and morphological development of differentiating aNPCs, suggesting that Wnt5a may control the development of new neurons in the adult brain.

**Disclosures: S.B. Arredondo:** None. **F. Guerrero:** None. **J. Jensen-Flores:** None. **D.B. Bustamante:** None. **L. Varela-Nallar:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

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**Program#/Poster#:** 461.10/B28

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** HHMI

NIH

Helen Hay Whitney Postdoctoral Fellowship

NSF Postdoctoral Fellowship

**Title:** Developmental characterization of human induced neurons

**Authors: *L. GIAM**, X. DU, I. T. HULL, T. C. SUDHOF
Stanford Univ., Stanford, CA

**Abstract:** Our lab recently reported that a single transcription factor (Neurogenin-2) can drive the differentiation of human embryonic stem cells into functional induced neurons (iNs) over several weeks. These iNs express synaptic markers at both transcript and protein levels and exhibit electrophysiological properties of excitatory neurons. This reduced system presents many opportunities, but in order to be useful for genetic screens and manipulations, we must understand the transcriptomic and proteomic profiles of these neurons in both immature and mature states. We developed strategies to culture pure iNs that were functionally equivalent to previous iNs grown on mouse glial cells in order to label proteins quantitatively using stable isotope labeling of amino acids (SILAC) and conduct RNAseq.

**Disclosures: L. Giam:** None. **X. Du:** None. **I.T. Hull:** None. **T.C. Sudhof:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.11/B29

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** CAPES, BEX 1279-13-0

**Title:** Global gene expression changes associated with neuronalisation of the cortically-derived neural stem cell line CTX0E16: Potential implications for neurodevelopmental diseases

**Authors: *R. R. DUARTE**[1], T. R. POWELL[1], G. ANDERSON[1], D. F. NIXON[2], G. BREEN[1], S. LEE[1], R. M. MURRAY[1], N. J. BRAY[3], D. P. SRIVASTAVA[1]
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**Abstract:** **INTRODUCTION** The human neural progenitor cell line CTX0E16 is a robust source of forebrain-like glutamatergic cortical neurons that display intrinsic functional properties (Anderson et al., 2015). This cell line was obtained from the embryonic cortex of a 12-week gestation XY fetus, and conditionally immortalised by ectopic expression of the c-Myc$^{ER\ TAM}$ transgene (Pollock et al, 2006). This construct allows the stem cells to be maintained in a proliferative stage under the presence of hydroxytamoxifen (4-OHT) and certain trophic factors in the medium, while removal of 4-OHT and maintenance of cells in a differentiation medium will stimulate neuronalisation. Understanding the global gene expression changes occurring during neuronalisation of this *in vitro* model, and their relationship with genetic association studies of schizophrenia and autism, might reveal clues to the biological processes impaired in these neurodevelopmental diseases. **METHODS** The CTX0E16 cell line was provided by ReNeuron (www.reneuron.com) through a Material Transfer Agreement. Total RNA was extracted from neural progenitor cells (NPCs) and from cells submitted to the neuronalisation protocol during 28 days (DD28) (n=3) (Anderson et al., 2015). DNA-free RNA samples were submitted to the IoPPN Genomics & Biomarker Core Facility for analysis in the Illumina HT12 v4 chip. Raw fluorescence probe intensity values were extracted using GenomeStudio, and subsequently background-corrected and log-transformed in R using the lumi package. Genes differentially expressed (t-test) at a false-discovery rate < 0.05 (FDR, q-value < 0.05) were submitted to Weighted correlation network analysis (WGCNA) and gene ontology (GO) analysis. MAGMA was used to investigate, in the list of differentially expressed genes, a potential enrichment for genes previously implicated in schizophrenia and autism by genome-wide association studies (GWAS). **HYPOTHESIS** Our assumption is that neurodevelopmental diseases such as schizophrenia and autism might share a genetic component with processes driving early cortical maturation, which can be modelled *in vitro*. **EXPECTED RESULTS** We

expect to identify and annotate sets of genes involved in cortical maturation that are additionally involved in the aetiology of schizophrenia and autism, which, furthermore, are believed to be disturbed in these diseases.

**Disclosures:** **R.R. Duarte:** None. **T.R. Powell:** None. **G. Anderson:** None. **D.F. Nixon:** None. **G. Breen:** None. **S. Lee:** None. **R.M. Murray:** None. **N.J. Bray:** None. **D.P. Srivastava:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.12/B30

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Molecular and functional characterization of hiPSCs derived dopaminergic neurons

**Authors: *C. ÜBERBACHER**
EURAC Res., Bolzano, Italy

**Abstract:** Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by loss of dopaminergic (DA) neurons in the *substantia nigra pars compacta* and by intracellular inclusions (Lewy bodies) in surviving neurons. The focal loss of neurons makes the disease particularly interesting for the stem cell field as it makes it an attractive target for patient derived cell substitution therapy. Therefore, in the recent years iPSCs have become a very important resource for the *in vitro* generation of a cell model of PD.
Current standard protocols for defining maturity of iPSC derived DA neurons are illustrating expression of Tyrosine Hydroxylase (TH) along with varying midbrain markers like Lmx1a/b, FOXA2 and OTX2, paired with firing of action potentials of TH positive neurons. However, despite showing primary function of neurons as in the transduction of a chemoelectrical signal, positive electrophysiological identification of these cells are limited to single action potentials, lacking the display of synaptic function.
We aim to address the electrophysiological development of iPSC derived DA neurons, using an established differentiation protocol (Kriks *et al*.). Under these conditions, we observed expression of molecular and functional characteristics of DA identity including expression of FOXA2, LMX1A, TH and PITX3. We also observe co-staining of TH with GIRK2 channel, a feature of A9 DA neurons, the subtype most susceptible to degeneration in PD. Additionally, we will supplement this protocol to accelerate this neuronal development, with particular attention to synapse function.
We tracked the markers expression over time to understand the timing of midbrain DA neuron cell faith definition. The maturation process of cells was monitored throughout the differentiation by staining for markers of mature DA neurons (NURR1, MAPT/Tau) and synapse formation

(PSD95, Synaptophysin) by Western Blot and immunocytochemical assays as well as qRT-PCR for monitoring transcriptional activation.
To assess neuronal properties, whole-cell patch clamp recordings are obtained from neurons, measuring spontaneous and evoked action potentials, $Na^+$-, $K^+$-and $Ca^{2+}$ mediated currents and miniature excitatory post-synaptic currents.
Finally, we assess expression of Dopamine Transporter (DAT), Aromatic L-amino acid decarboxylase (AADC) and TH by immunocytochemistry over time and monitor stimulated DA release by MS-HPLC analysis of the culture media.
The data presents a thorough characterization of an *in vitro* derived neuronal model that could allow a better understanding of maturation process of iPSC derived DA neurons.

**Disclosures: C. Überbacher:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.13/B31

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** CAPES

CNPq

**Title:** Lineage reprogramming of astroglia into different neurons

**Authors: *M. CHOUCHANE**[1], A. FARIAS[2], D. MOURA[1], M. HILSCHER[3], R. LEAO[2], M. COSTA[2]
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**Abstract:** Astroglial cells isolated from the rodent postnatal cerebral cortex are particularly susceptible to lineage reprogramming into neurons. However, it remains unknown whether other astroglial populations retain the same potential. Likewise, little is known about the fate of induced neurons (iNs) *in vivo*. In this study we addressed these questions using two different astroglial populations isolated from the postnatal brain reprogrammed either with *Neurogenin-2* or *Achaete scute homolog-1*. We show that cerebellum (CerebAstro) and cerebral cortex astroglia (CtxAstro) generates iNs with distinctive neurochemical and morphological properties. Both astroglial populations contribute iNs to the olfactory bulb following transplantation in the postnatal and adult mouse subventricular zone. However, only CtxAstro transfected with Neurog2 differentiate into pyramidal-like iNs after transplantation in the postnatal cerebral

cortex. Altogether, our data indicate that the origin of the astroglial population and TF used for reprogramming, as well as the region of integration, affect the fate of iNs.

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**Poster**

**461. Stem Cell Applications and Neural Reprograming**

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**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIH/NINDS-NS088095

NS092616

The Welch Foundation

The Decherd Foundation

**Title:** A role of the SHH-GLI pathway in neuronal reprogramming in the adult mouse spinal cord

**Authors: *L. WANG**, C.-L. ZHANG
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**Abstract:** Regeneration of new neurons may provide the much needed cells for neural repair after traumatic injury to the central nervous system. We recently showed that the stem cell factor SOX2 is sufficient to in vivo reprogram the reactive glial cells to mature neurons in both the adult mouse brain and spinal cord. SOX2-mediated in vivo reprogramming passes through ASCL1+ neuroprogenitors and DCX+ neuroblasts prior to neuronal maturation. This reprogramming process is further regulated by the p53-p21 pathway through controlling cell cycle progression. In current study, we examined additional signaling pathways for their role in determining regional identity and subtypes of reprogrammed spinal neurons. We found that the SHH-GLI pathway greatly influences the activity of induced neuroprogenitors and neuroblasts in a region-specific manner. Different components of this pathway exhibit differential regulation on the reprogramming process. Through genetic lineage mapping and rabies-mediated tracing, we are further examining the role of SHH-GLI signaling on subtypes and neural networks of the reprogrammed neurons in the adult spinal cord. The results of this study may contribute to the molecular insights into the in vivo reprogramming process and provide a foundation for future clinical translation of neural regeneration-based therapies.
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**KEY WORDS:** *in vivo* reprogramming, SOX2, neurogenesis, SHH, GLI

**Disclosures: L. Wang:** None. **C. Zhang:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

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**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIH Grant U01MH103365-03

**Title:** Comparative transcriptome and gene regulation in iPSC-derived organoids and donor-identical brain tissue

**Authors: *S. SCUDERI**[1], A. AMIRI[1], G. COPPOLA[1], F. WU[1], D. FRANJIC[2], N. SESTAN[5], M. GERSTEIN[3], S. WEISSMAN[4], A. ABYZOV[6], F. M. VACCARINO[1]
[1]Child Study Ctr., [2]Neurosci., [3]Mol Biophys & Biochem, [4]Genet., Yale Univ., New Haven, CT; [5]Yale Univ. Sch. Med., New Haven, CT; [6]HSR, Harwick 3-12, Mayo Clin., Rochester, MN

**Abstract:** Modeling human brain development *in vitro* is critically important to improve our understanding of neuropsychiatric disorders. As part of the PsychENCODE project, we generated human induced pluripotent stem cells (hiPSCs)-derived neural organoids to study early genetic programs in forebrain development and define to what extent they can recapitulate human embryonic and fetal brain development. We established iPSC lines from skin fibroblasts of three human prenatal brain specimens and two clones per specimen were differentiated into telencephalic organoids over a time course (TD 0, TD 11, TD 30). We examined transcriptomes and gene regulatory regions in the temporal series of hiPSCs-derived organoids as compared to donor-identical brain tissue from ventricular/subventricular zone and cortical plate. To this end, we utilized RNA- and histone chromatin immunoprecipitation (ChIP)-sequencing. The organoids were characterized by immunocytochemistry and qPCR, and expression of radial glial markers and mature cortical neurons confirmed telencephalic fate. Hierarchical clustering of the organoids' transcriptomes demonstrated stage-specific clustering according to time course of *in vitro* development. Mapping organoids' transcriptomes against the BrainSpan dataset suggested highest correlations with neocortex and showed their progressive maturation *in vitro* across time, corresponding to post-conceptional weeks 8-16 of human fetal development. We then inferred transcriptional alterations, by differential gene expression, between each time point and the two brain regions analyzed. We found, as expected, a large number of differentially expressed genes (~5000) between TD 0 and brain, and a decreasing number at TD 11 and TD 31, suggesting a stronger, albeit incomplete similarity of the organoids at the later time points, consistent with the

previous classification. In parallel, we studied differences in epigenetic regulation by performing ChIP-seq, to identify promoters and enhancers of active genes at different developmental stages. Hierarchical clustering of H3K27ac and H3K4me3 peaks demonstrated clustering of organoids with fetal brain samples from our and external databases, whereas adult brain samples formed a separate cluster. Differential peak detection followed by gene ontology analysis revealed that, along differentiation, genes associated with increased H3K4me3/H3K27ac levels are involved in nervous system development while genes associated with decreased H3K4me3/H3k27ac levels are more relevant to cell cycle. These data suggest that organoids recapitulate transcriptome and epigenome features of fetal human brain.

**Disclosures:** **S. Scuderi:** None. **A. Amiri:** None. **G. Coppola:** None. **F. Wu:** None. **D. Franjic:** None. **N. Sestan:** None. **M. Gerstein:** None. **S. Weissman:** None. **A. Abyzov:** None. **F.M. Vaccarino:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

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**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIH R43 DA042659

**Title:** Generation and rapid maturation of cortical layer V glutamatergic neurons from human iPSCs

**Authors: B. DUNGAR**, K. XU, M. HENDRICKSON, *Z.-W. DU
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**Abstract:** Numerous neurological and psychiatric disorders involve glutamatergic neurons specific to one or more of the six cortical layers. Death or malfunction of these specific neurons underlies disease pathophysiology and disrupts higher cognitive function. Study of these neurons may reveal the molecular mechanisms behind their vulnerability and enable development of more relevant disease models. Toward this goal, we developed protocols to efficiently produce layer V cortical glutamatergic neurons. Both normal and patient iPSCs were first induced to a neural fate and then patterned to glutamatergic neuronal progenitors (>90% SOX1+/PAX+). Using novel combinations of small molecules, the late-stage progenitors can be expanded up to 500-fold, which allows for production of large and consistent batches of neurons. Finally, the progenitors were plated in medium containing a specialized maturation supplement that rapidly yields morphological and functional maturation. After treating with this cocktail, neurons displayed extensive neurite outgrowth within 3 days, expressed pre- and post-synaptic mature markers within 7 days, and exhibited electrophysiological activity within 2 weeks. Seven days

post-plating, the cultures were >90% neurons (MAP2+) with the following breakdown by layer identity: ~90% layer V (CTIP2+/ FOXP2-/ SATB2-), ~8% layer VI (FOXP2+), and ~2% layer II-IV (SATB2+). Thus, our novel differentiation protocol generates a pure neuronal culture that is highly enriched for cortical glutamatergic neurons with a layer V identity. Coupled with the ability to generate very large batches (>1 billion neurons) and bring about rapid maturation, layer V cortical neurons present a highly relevant model system for drug discovery and development.

**Disclosures:** **B. Dungar:** A. Employment/Salary (full or part-time):; BrainXell, Inc. **K. Xu:** A. Employment/Salary (full or part-time):; BrainXell, Inc. **M. Hendrickson:** A. Employment/Salary (full or part-time):; BrainXell, Inc. **Z. Du:** A. Employment/Salary (full or part-time):; BrainXell, Inc..

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

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Orchard Foundation

**Title:** Optimization of factors in protocols to differentiate iPSCs to midbrain dopamine neurons for Parkinson's disease

**Authors: *T. M. OSBORN**[1], R. THOMAS[1], D. DINESH[1], E. FERRARI[1], J. A. KORECKA[1], J. PRUSZAK[2], O. ISACSON[1], P. J. HALLETT[1]
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**Abstract:** Parkinson’s disease (PD) is a chronic progressive neurodegenerative disease in which dopaminergic neurons originating in the substantia nigra degenerate, resulting in loss of motor control. Treatment with L-DOPA can initially restore dopaminergic (DA) levels and motor function, but does not treat the disease. At the onset of symptoms and diagnosis about 70% of the midbrain DA neurons have degenerated, at which stage treatment with therapeutics to prevent cell loss is too late. Instead, neural transplantation with midbrain dopamine neurons can

specifically replace the DA cell population and provide functional motor benefits in patients with PD. The use of pluripotent stem cell derived neurons provides the opportunity to overcome current limitations posed by fetal donor tissue in PD. For this approach, robust and reproducible protocols for differentiation of pluripotent stem cells toward ventral midbrain dopaminergic fates are essential. We have previously published two differentiation protocols that generate midbrain dopaminergic neurons (Cooper O. et al., Mol Cell Neurosci. 2010 Nov;45(3):258-66 and Sundberg M., et al., Stem Cells. 2013 Aug;31(8):1548-62). Our recent efforts have led to an efficient xeno-free and feeder-free protocol that we have successfully 1) transplanted into 6-OHDA lesioned rats using both a fresh and frozen-thawed cell preparation, with successful graft survival and behavioral recovery, 2) used for autologous transplants in parkinsonian primates and 3) used in vitro in cell vulnerability and drug-discovery studies. Here we have compared factors commonly used in protocols for differentiation of iPSCs into midbrain dopaminergic neurons and show that the ideal concentrations, timing of addition, as well as protein isoforms (FGF8a vs. FGF8b) differ depending on the underlying protocol and procedure. As the reality of using midbrain dopaminergic neurons derived from pluripotent stem cells for transplantation is getting closer to the clinic, an understanding and clarification of the differences in the protocols proposed for such use is essential.

**Disclosures: T.M. Osborn:** None. **R. Thomas:** None. **D. Dinesh:** None. **E. Ferrari:** None. **J.A. Korecka:** None. **J. Pruszak:** None. **O. Isacson:** None. **P.J. Hallett:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.18/B36

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Nrf2 as a biomarker of oxidative stress induced by rotenone in a human iPSC neuronal model

**Authors: *F. PISTOLLATO**, D. ZAGOURA, D. CANOVAS-JORDA, A. PRICE
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**Abstract:** Human induced pluripotent stem cells (hiPSCs) can be expanded and efficiently differentiated into different types of neuronal and glial cells, serving as test systems for toxicity testing and, in particular, for the assessment of different pathways involved in neurotoxicity. Here we show that hiPSC-derived neuronal cells can be used to measure the activation of the Nrf2 signaling pathway, a key regulator of the antioxidant-response-element-(ARE)-driven cellular defence mechanism against oxidative stress. Our data indicate that both an acute and repeated dose treatment with rotenone, an inhibitor of mitochondrial complex I and an inducer of

Parkinson-like features can elicit activation of Nrf2, leading to an induction of astrocyte activation, reduction of neurite length and dopaminergic neuronal cell death. These data suggest that this hiPSC model can be applicable to the new toxicity testing paradigm, in which chemicals are assessed based on their ability to perturb biological pathways.

**Disclosures: F. Pistollato:** None. **D. Zagoura:** None. **D. Canovas-Jorda:** None. **A. Price:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.19/B37

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Role of FKBP5 disinhibition in neuronal development: Cerebral organoids as a model for stress-related disorders

**Authors: *S. MARTINELLI**, C. CRUCEANU, R. DI GIAIMO, C. KYROUSI, S. CAPPELLO, E. B. BINDER
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**Abstract:** Introduction
FKBP5 is best known as a co-chaperone of the glucocorticoid receptor (GR), involved in the regulation of the hypothalamic-pituitary-adrenal (HPA)-axis. GR activation induces FKBP5 expression, which, on one side, leads to the inhibition of the GR itself and, on the other, regulates a plethora of cellular pathways including neural-specific ones. Several studies have demonstrated that increased levels of FKBP5 in the context of gene x early adversity interactions (GxE) correlate with a number of stress-related disorders. Furthermore, postmortem studies have found increased FKBP5 levels in several brain regions in a number of psychiatric disorders. These human findings have been corroborated by studies in animal models, but due to the difficulty in accessing human neural tissue, studies in human have mainly been limited to non-neuronal samples.
Aim
The aim of this project is to investigate, in a human neuronal system, the effect of FKBP5 disinhibition on neuronal differentiation and development to better understand the molecular and cellular mechanisms that link GxE to the onset of psychiatric disorders.
Methods
We use human induced pluripotent stem cells (hiPSC) reprogrammed from fibroblasts. hiPSC are differentiated into neural progenitor cells (NPC) and mature neurons and to generate cerebral organoids in accordance to the Lancaster and Knoblich protocol (2014). FKBP5 expression is assessed at the RNA level using qPCR, RNA seq and a quantitative fluorescent based in situ

hybridization system. At the protein level, we use immunohistochemistry (IHC) and western blot. Neuronal maturation is assessed using specific pluripotency and differentiation markers. To mimic external stressors, we treat the cells and organoids at different maturation stages with dexamethasone (dex), a GR agonist.
Results
Consistently with the literature, we observed low levels of FKBP5 expression across neuronal differentiation. With dex treatment, RNA levels of FKBP5 increased in both NPC and mature neurons. Interestingly, with IHC, we observed a marked increase specifically in the germinal zone of dex-treated organoids.
We are currently proceeding with the overexpression of FKBP5 in organoids, by co-electroporating FKBP5 and GFP expressing plasmids into ventricles and analyzing the differences in migration and maturation of neural progenitors and radial glial cells.
Conclusion
FKBP5 is expressed in iPSC derived neuron and brain organoids and regulated by glucocorticoids. These systems may thus present interesting models to investigate the impact of enhanced FKBP5 expression on neuronal development and differentiation.

**Disclosures: S. Martinelli:** None. **C. cruceanu:** None. **R. Di Giaimo:** None. **C. Kyrousi:** None. **S. Cappello:** None. **E.B. Binder:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.20/B38

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIH Grant RO1 EY024940

Indiana Department of Health

**Title:** Extensive axonal outgrowth and pathfinidng from retinal ganglion cells derived from human pluripotent stem cell-derived retinal organoids

**Authors: *C. FLIGOR**[1], A. SRIDHAR[3], K. LANGER[2], Y. REN[4], V. M. SLUCH[6], D. ZACK[7], D. M. SUTER[5], J. S. MEYER[1]
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**Abstract:** Retinal ganglion cells (RGCs) serve as a vital connection between the eye and the brain and as such, degenerative diseases and injuries which cause the loss of RGCs often lead to blindness. Human pluripotent stem cells (hPSCs) are attractive candidates for cell replacement therapies, due to the ability to direct their differentiation into any desired cell type, including RGCs. However, in order for successful replacement of RGCs to occur, axons must extend across significant distances to reach their targets. Additionally, once this axonal pathfinding is accomplished, these axons must also be able to form functional synaptic connections. Significant obstacles remain before the implementation of hPSC-derived RGCs for cell replacement. The development of a reliable in vitro model of RGC development and axonal outgrowth would allow for the direct examination of those factors influencing axonal outgrowth and connectivity, with the goal of eventually translating these findings into customized strategies for cell replacement in vivo. As such, efforts thus far have focused on the development of effective and reliable assays with which to test the ability of hPSC-derived RGCs to extend axons in response to a variety of extrinsic cues. Initially, RGCs were characterized by immunocytochemistry for the expression of several RGC-associated markers. Growth cones were observed at the leading edge of extending neurites, with these growth cones enriched for F-actin and expressing receptors essential for axonal pathfinding. Live imaging revealed growth cones that were highly dynamic and motile over time. Subsequently, the ability to enhance RGC neurite outgrowth was analyzed in response to multiple factors, including varying substrates, culture media and growth factors. Enriched populations of RGCs were isolated and plated to allow for neurite outgrowth, with significant outgrowth observed within the first 24 hours. Optimized assays allowed for neurite growth over 1mm in this time. The results of this study demonstrate the robust ability of hPSC-derived RGCs to extend axons over long distances. hPSC-derived retinal organoids recapitulate the stratification of the human retina and produce RGCs with expected phenotypes. Opportunities exist by which to control the directionality of axonal outgrowth as well. Finally, RGC axons and growth cones are significantly influenced by substrate composition and growth factor signaling. Overall, these results will facilitate the replacement of RGCs following their loss due to disease and degeneration, as extensive axonal outgrowth will be critical for the development of personalized transplant therapies for optic neuropathies.

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**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.21/B39

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** Center for Neuroscience and Regenerative Medicine Grant G1703898

Uniformed Services University Grant R070301115

**Title:** Improved functional maturation of induced pluripotent stem cell-derived neurons with neonatal mouse astrocyte co-culture, forced cell cycle exit and enhanced GABA and calcium signaling

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**Abstract:** Human induced pluripotent stem (iPS) cell-derived neurons and astrocytes are attractive cellular tools for nervous system disease modeling and drug screening. Optimal utilization of these tools requires differentiation protocols that efficiently generate functional cell phenotypes in vitro. As nervous system function is dependent on networked neuronal activity involving both neuronal and astrocytic synaptic functions, we examined astrocyte effects on the functional maturation of neurons from human iPS cell-derived neural stem cells (NSCs). We first demonstrate human iPS cell-derived NSCs can be rapidly differentiated in culture to either neurons or astrocytes with characteristic cellular, molecular and physiological features. Although differentiated neurons were capable of firing multiple action potentials (APs), few cells developed spontaneous electrical activity in culture. We show spontaneous electrical activity was significantly increased by neuronal differentiation of human NSCs on feeder layers of neonatal mouse cortical astrocytes. In contrast, co-culture on feeder layers of isogenic human iPS cell-derived astrocytes had no positive effect on spontaneous neuronal activity. Forced cell cycle exit and enhanced GABA and calcium signaling further increased the frequency of spontaneous electrical activity and multiple AP firing in co-cultured human neurons. Spontaneous electrical activity was dependent on glutamate receptor-channel function and occurred without changes in $I_{Na}$, $I_K$, $V_m$ and AP properties of iPS cell-derived neurons. These data demonstrate co-culture with neonatal mouse cortical astrocytes but not human isogenic iPS cell-derived astrocytes stimulates glutamatergic synaptic transmission between iPS cell-derived neurons in culture. We present RNA-sequencing data for an immature, fetal-like status of our human iPS cell-derived astrocytes as one possible explanation for their failure to enhance synaptic activity.

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**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.22/B40

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIH NIDCD R01-DC010844

NIH P30-DC005983

NIH R21-DC016157

**Title:** Vascular regeneration by reprogramming of ng2-derived angiogenic cells in the inner ear

**Authors: *X. SHI, Dr.**, X. WANG
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**Abstract:** Can damaged or degenerated vessels be regenerated in the ear? The question is important as disruption of cochlear blood flow is seen in a wide variety of hearing disorders including loud sound-induced hearing loss (*endothelial injury*), ageing-related hearing loss (lost vascular density), and genetic hearing loss (i.e.,Norrie disease: *strial avascularization*). Progression in CBF pathology can parallel progression in hair cell and hearing loss. However, new vessel growth in the ear has not been studied, nor has the role of angiogenesis in hearing. In this study, using a vascular damage model created by depleting pericytes (PC) in the cochlea which is in conjunction with an established ex vivo tissue explant mode, we demonstrate for the first time that damaged vascular function (blood labyrinth barrier) can be restored by activating the vascular endothelial growth factor signal. Moreover, using transgenic neural/glial antigen 2 (NG2) fluorescent reporter mice, we have shown the progenitors of "*de novo*" strial vessels are pre-existing ECs and converted perivascular NG2-derived cells. Most important, the pattern of the newly formed vessels resembles the natural 'mesh pattern' of *in situ* strial vessels, with both lumen and expression of tight junctions. Taken together, our data shows that damaged strial microvessels can be regenerated by reprogramming of NG2-derived angiogenic cells. The restoration of functional vasculature may be crucial for restoration of vascular dysfunction related hearing loss.

**Disclosures: X. Shi:** None. **X. Wang:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.23/B41

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NSERC M3

**Title:** An elite model of reprogramming - Neural Crest cells are the preferred origin for cell Reprogramming

**Authors: *A. FAHMY**[1], J. XU[2], I. BROKHMAN[3], B. L. COLES-TAKABE[1], D. J. VAN DER KOOY[4]
[1]Mol. Genet., [3]prof. van der Kooy lab, [2]Univ. of Toronto, Toronto, ON, Canada; [4]Dept Med. Genet, Univ. Toronto, Toronto, ON, Canada

**Abstract:** The discoveries made by Yamanaka et al and other groups in reprogramming somatic cells either to pluripotent stem cells (called induced pluripotent stem cells, or iPSCs) or directly to other differentiated cells has opened a new field in stem cell research. However, these reprogramming techniques are plagued by problems relating to the efficiency of the process and the poor understanding of their cellular mechanisms. Several studies were able to improve the efficiency of reprogramming by manipulating chromatin remodeling factors. Despite this there is still no clear and non-ambiguous study which shows if all differentiated cells have the potential of being reprogrammed or whether there exists an elite subpopulation of cells that are selectively being reprogrammed. We hypothesise that a primary source of iPSCs and directly reprogrammed cells are neural crest stem cells (NCSCs) found in culture. It is well established that multipotent NCSCs migrate to many parts of the developing embryo where they can produce a vast array of cell types; some of these NCSCs remain as undifferentiated stem cells throughout adulthood. We traced the lineage of neural crest cells in mice embryos using a Wnt1-Cre and ROSA-TdTomato reporter system. We found that YFP positive cells (NC derived) were present in the primary cell culture and they increased in proportion with passage number. This shows that there exists neural crest derived cells in cultures identical to those used in reprogramming studies. We reprogrammed skin samples of mouse embryonic fibroblasts (MEFs) and found that 100% of the iPSCs produced were YFP positive (from NC origin). In cell populations that have been sorted for NC derived and non-NC derived cells, we observed that the NC pure population reprogrammed at an efficiency 10-fold higher, while very few non-NC cells were able to reprogrammed to iPSCs (albeit at a lower efficiency when compared to unsorted populations). Despite the fact that some of the iPSC colonies were produced from non-NC cells, this may not suggest that some non-NC cells also are reprogrammed, as the efficiency of the cre labeling may not be 100%. The same results have been observed when reprogramming skin cells to neurons

using three neuronal transcriptional factors (Brn2, Ascl1, Myt1l). These studies can help better understand the cellular mechanism of reprogramming and will help devise more efficient techniques of reprogramming that could contribute to new therapies for treating neurodegenerative diseases.

**Disclosures: A. Fahmy:** None. **J. Xu:** None. **I. Brokhman:** None. **B.L. Coles-Takabe:** None. **D.J. Van Der Kooy:** None.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.24/B42

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Calcium handling assays with human iPSC-derived neuronal cell types

**Authors: K. KIM**[1], K. MANGAN[1], M. HANCOCK[1], *K. OELSTROM[1], S. DU[2], C. CARLSON[1]
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**Abstract:** Human cell types differentiated from induced pluripotent stem cells (iPSC) offer an attractive source of cellular material for both toxicity screening and drug discovery because of the biologically relevant systems they can represent *in vitro*. In combination with cutting-edge instrumentation, iPSC-derived cells be used to explore functionality of human cells and to identify phenotypes for disease modeling. The FDSS uCell from Hamamatsu is a kinetic plate reader that is equipped with a high speed camera, an integrated dispenser head, and electrical field stimulation capability that enables intracellular ion measurement in live neuronal cell type. In this poster, we highlight the development of cell-based assays on the FDSS uCell to measure calcium handling in human iPSC-derived neurons. Specifically, we utilized GABAergic, glutamatergic, and dopaminergic neurons in both mono-culture and co-culture with iPSC-derived astrocytes. Addition of agonists that activate excitatory receptors, such as AMPA-R, Glutamate receptor, and NMDA-R, result in robust responses in calcium flux. Furthermore, we have also developed a method to measure spontaneous calcium oscillations, most importantly in iPSC-derived glutamatergic neurons, where these cells have been used to test the effects of various small-molecules as potentially seizurogenic. Finally, we have also leveraged the power of iPSC technology to illustrate phenotypic data from disease-specific or patient-derived samples, including a mutant KCNT1 channel that represents a rare but severe epilepsy syndrome. Taken together, these examples should help to create new avenues for safety assessment and toxicology studies, as well as serve as a template for future opportunities in modeling disease with human iPS cells.

**Disclosures:** **K. Kim:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **K. Mangan:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **M. Hancock:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **K. Oelstrom:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **S. Du:** A. Employment/Salary (full or part-time):; Hamamatsu. **C. Carlson:** A. Employment/Salary (full or part-time):; Cellular Dynamics International.

**Poster**

**461. Stem Cell Applications and Neural Reprograming**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 461.25/B43

**Topic:** I.01. Molecular, Biochemical, and Genetic Techniques

**Support:** HIAS 15004

**Title:** Differentiation and enrichment of subtypes of cortical interneurons using human induced pluripotent stem cell derived serum free embryoid bodies

**Authors: *R. M. DERANIEH**, M. W. NESTOR
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**Abstract:** Background: Dysfunction of interneurons is implicated in several neurodevelopmental disorders including epilepsy, schizophrenia, bipolar disorder and autism. Interneurons play an important role in modulating circuit function. The effect of interneurons on circuits is dependent on the subtype specificity of these cells. The calcium-binding protein expressing neurons, including calbindin (CB), calretinin (CR), and parvalbumin (PV)-positive neurons make up major classes of interneurons in the brain. The underlying mechanism whereby they elicit their effect in cortical circuity that has been built using human induced pluripotent stem cells (hiPSCs) is not well understood. This is largely due to the lack of an efficient process for generating subtypes of interneurons. Although much progress has been made in the past few years, current protocols generate mixed neuronal cultures, often involving forced expression, and only a small percentage of interneurons are generated.
Objective: Here, we demonstrate a novel approach to differentiate and enrich for specific subtypes of human interneurons.
Methods: Using hiPSCs, serum free embryoid bodies (SFEBs) were generated and induced using standard dual-SMAD inhibition combined with placement of the SFEBs on Millipore Organotypic inserts (Nestor et al., 2013). After placement, SFEBs were differentiated for 3-4 weeks. Interneurons were isolated using magnetic activated cell sorting, after which the neurons were allowed to recover for 2 weeks on poly-L-ornithine and laminin.
Results: Quantification analysis demonstrated substantial enrichment for CB, CR, and PV

positive neurons and a 2-fold increase in their numbers in comparison to populations generated in conventional 2D cultures.
Conclusions: This approach will facilitate the study of subtype-specific human interneurons to answer questions pertaining to the mechanism(s) that underlie the pathophysiology of several neurodevelopmental disorders. It also offers the potential to identify novel drug targets for the development of therapeutics for the treatment of these disorders.

**Disclosures: R.M. Deranieh:** None. **M.W. Nestor:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.01/B44

**Topic:** A.07. Developmental Disorders

**Title:** Temporal processing deficits and other behavioral abnormalities in the valproic acid model of autism spectrum disorder

**Authors: *W. E. DECOTEAU**[1,2], E. BRETON[2], M. DEMERS-PEEL[1], E. L. MORGAN[1], A. M. NICHOLSON[2], S. PALIC[2], C. J. POULIN[1], A. ROBINSON[2], S. SIKANDAR[3], A. E. FOX[1,2]
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**Abstract:** Autism spectrum disorder (ASD) is a highly heterogeneous neuro-developmental disorder classically characterized by communication deficits, repetitive behaviors, and difficulties with social interactions. Recently it has been proposed that this broad array of impairments may be reflect a more fundamental, underlying, disruption in timing and time perception. However, studies of temporal processing in ASD individuals have produced mixed results. Animal models have served as a valuable tool for elucidating behavioral and neurobiological mechanisms of ASD. Valproic Acid (VPA) is an environmental toxin that has been linked to ASD. The VPA rodent model has become one of the most widely used animal analogues of ASD. Here, we examined whether *in utero* exposure to VPA can generate specific behavioral deficits related to temporal processing. Pregnant rats were exposed to VPA (500mg/kg, i.p.) on gestation day 12.5. Pups from each group were weaned and temporal processing was tested using temporal bisection, peak interval, and impulsive choice tasks. In addition, the rats were assessed on a battery of standard behavioral tests that measured motor function, perseverative and exploratory behavior, anxiety, memory, and social interactions. Across the three temporal processing tasks, the VPA group was more heterogeneous, with a subgroup of animals showing decreased response inhibition on the timing tasks and lack of sensitivity to delay in the impulsive choice task, compared to controls. On the other behavioral tasks, VPA animals demonstrated normal performance on the motor and memory tasks, but were significantly different from control animals on some measure of perseveration, anxiety, and

social interaction. These findings have important implications for characterizing the behavioral abnormalities of the VPA model and understanding the temporal processing dynamics observed in humans with ASD.

**Disclosures: W.E. DeCoteau:** None. **E. Breton:** None. **M. Demers-Peel:** None. **E.L. Morgan:** None. **A.M. Nicholson:** None. **S. Palic:** None. **C.J. Poulin:** None. **A. Robinson:** None. **S. Sikandar:** None. **A.E. Fox:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.02/B45

**Topic:** A.07. Developmental Disorders

**Support:** Canadian Institute of Health Research (CIHR) Team Grant (TEC-128094)

**Title:** Epigenetics, DNA methylation, and potential biomarkers for fetal alcohol spectrum disorders

**Authors: S. AMIRI**, C. OLSON, W. XU, G. HICKS, J. R. DAVIE, *M. RASTEGAR
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**Abstract:** Epigenetics control gene expression and cellular identity through orchestrated molecular events that are not directly reflected by the genomic DNA sequences. Recent discoveries have highlighted the importance of epigenetic modifications in brain development, neuroscience, and mental health. Such mechanisms include histone post-translational modifications (PTMs), DNA methylation, the action of regulatory RNA molecules, and chromatin remodelling, among others. While histone PTMs constitute the most diverse type of epigenetic modifications, DNA methylation is perhaps the best-studied epigenetic modification that links environmental factors to neuroscience and mental health.
Fetal Alcohol Spectrum Disorders (FASD) refer to a broad spectrum of neurodevelopmental disorders of the brain that are caused by prenatal alcohol exposure. FASD is a life-long disorder that is associated with mental disability, facial abnormalities, impaired cognitive and behavioural symptoms. Through a collaborative team effort, we aim for a combination of genome-wide and candidate gene approach to study the role of DNA methylation in deregulated gene expression program of brain-derived neural stem cells along with *in vivo* studies in mice, in order to identify potential biomarkers for FASD. Such biomarkers are critically important for the diagnosis of FASD cases, where the patient does not show any facial characteristics of FASD.
FASD is one the most common neurodevelopmental disorders in the Western World with a frequency of 1-2% and over 6 billion dollars spending per year (only in Canada) for FASD-associated health-related cost and productivity-loss in the affected individuals. Currently, FASD

has no cure or effective therapy strategy. Identification of potential FASD biomarkers is critically important for early detection of the disease for intervention strategies during the time period that the brain is still under development.

**Disclosures: S. Amiri:** None. **C. Olson:** None. **W. Xu:** None. **G. Hicks:** None. **J.R. Davie:** None. **M. Rastegar:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.03/B46

**Topic:** A.07. Developmental Disorders

**Support:** Department of Defence

Simons Foundation

NARSAD

NIH

The Nancy Lurie Marks Family Foundation

**Title:** Maternal antibodies in Autism spectrum disorder: Toward protection studies

**Authors: *L. BRIMBERG**[1], S. MADER[2], D. COMOLETTI[3], P. HUERTA[2], B. VOLPE[2], B. DIAMOND[2]
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**Abstract:** The concept that the in utero environment, and specifically maternal antibodies, can contribute to the development of Autism spectrum disorders (ASD) has been entertained for over a decade, but only recently have specific antibodies been identified. Studies, including our own, have shown that significantly more mothers of children with ASD have brain-reactive antibodies than controls. The hypothesis is that these anti-brain antibodies exploit a natural mechanism of immune protection of the fetus, cross the placenta, and, at a time when the fetal brain is not protected by a competent blood brain barrier, they perturb fetal brain development. To study the antigenic specificities of maternal brain-reactive antibodies and their contribution to ASD pathogenicity, we generated brain-reactive monoclonal antibodies from B cells of women with a child with ASD. We focused on a monoclonal antibody found to bind the extracellular domain of contactin-associated protein-like 2 (Caspr2). Interestingly, anti-Caspr2 antibodies are frequent in

women with brain-reactive serology and a child with ASD. To address its pathogenicity, we intravenously administered either non-brain reactive control antibody B1 or C6 (anti-Caspr2) to pregnant mice on gestational day E13.5. We demonstrated that male but not female mice exposed in utero to the C6 monoclonal antibody display abnormal cortical development at E15.5 with a thinner cortical plate and a reduced number of proliferating cells. Decreased dendritic complexity of excitatory neurons and reduced numbers of inhibitory neurons in the hippocampus, are present in adult offspring. Moreover, they exhibit impairments in sociability, flexible learning, and repetitive behavior. We believe that this effect might cause by anti-Caspr2 antibody mediated internalization of AMPA receptors in fetal neurons. Our initial model is based on a single exposure to the antibody. To capture better the human condition we have generated a new model where anti-Caspr2 antibodies are present during gestation. Female mice were immunized with the extracellular portion of Caspr2. When they exhibited titers to Caspr2, they were housed with a male to generate timed pregnancies. Male fetuses of dams harboring anti-Caspr2 antibodies showed thinning of the cortical plate and reduced proliferating cells at E15.5 similar to our previous results in male fetuses exposed in utero to C6. This histopathology was not seen in fetuses of control mice. We are currently characterizing the behavioral phenotype of offspring born to dams immunized with Caspr2, and developing therapeutic strategies to block the harmful effect of the antibodies.

**Disclosures: L. Brimberg:** None. **S. Mader:** None. **D. Comoletti:** None. **P. Huerta:** None. **B. Volpe:** None. **B. Diamond:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.04/B47

**Topic:** A.07. Developmental Disorders

**Support:** SFARI

**Title:** Maternal factors promote autism-like behaviors in offspring

**Authors: *J. HUH**
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**Abstract:** Maternal immune activation (MIA) contributes to the development of autism-like phenotypes in both primate and rodent offspring. In humans, epidemiological studies suggest that exposure of fetuses to maternal inflammation increases the likelihood of developing Autism Spectrum Disorder (ASD). We recently reported that Th17 cells, $CD4^+$ T helper effector cells expressing inflammatory cytokines such as interleukin 17a (IL-17a), are required in pregnant mice to induce behavioral as well as brain pathologies in the offspring. However, it is unclear if

other maternal factors are required to promote MIA-associated phenotypes. Moreover, underlying mechanisms by which MIA leads to immune cell activation with a systematic increase of IL-17a are not well understood. Our recent data to address these questions will be discussed.

**Disclosures: J. Huh:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.05/B48

**Topic:** A.07. Developmental Disorders

**Support:** Hungarian Research and Development Fund Grant K116654

Hungarian Brain Research Program [KTIA_13_NAP-A-III/1]

Gedeon Richter plc. (RG-IPI-2016-TP10-0012)

**Title:** Maternal P2X7 receptors drive offspring autism-like behaviour in mice

**Authors: *B. SPERLAGH**, G. HORVÁTH, L. OTROKOCSI, Á. KITTEL
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**Abstract:** Maternal immune activation is a principal environmental risk factor contributing to neurodevelopmental psychiatric disorders, including autism spectrum disorder (ASD). Maternal infection is associated with the later emergence of ASD compromising foetal brain development at critical periods of pregnancy, and the elevation of maternal pro-inflammatory cytokines has been causally linked to perinatal brain reprogramming. However, the molecular signalling pathway that converts maternal immune activation to pathologically relevant neurodevelopmental abnormalities in the offspring has been unclear until now. The NLRP3 inflammasome signalling pathway, triggered by the co-activation of P2X7 purinergic receptors is an intracellular multiprotein complex responsible for the conversion of innate immune response to inflammation in response to exogenous and endogenous danger signals. Here we report that activation of maternal P2X7 receptors is necessary and sufficient to transduce maternal immune activation (MIA) to autistic phenotype in the offspring. We show that whilst maternal immune activation by poly(I:C) injections to pregnant wild-type mouse dams elicits autism-like phenotype in their offspring, including social deficit, impairment of sensorimotor coordination, repetitive behaviours, atrophy of cerebellar Purkinje cells and destruction of synapses, no such alterations are observed in mice genetically deficient in P2X7 receptors. The effect of P2X7 gene deficiency could be reproduced by maternal treatment with specific P2X7 receptor antagonist JNJ7965567 (20 mg/kg i.p.). Genetic deletion and pharmacological inhibition of maternal P2X7

receptors also effectively counteracted the induction of IL-6 in the maternal plasma and foetal brain, whilst postnatal P2X7 receptor inhibition alleviates behavioural and morphological alterations in the offspring. Our results offer a therapeutic possibility for early prevention and treatment of ASD, the increasingly prevalent psychiatric disorder in children.

**Disclosures: B. Sperlagh:** None. **G. Horváth:** None. **L. Otrokocsi:** None. **Á. Kittel:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.06/B49

**Topic:** A.07. Developmental Disorders

**Support:** NIH/NIEHS R01ES025549

**Title:** Prenatal air pollution and maternal stress alters brain development in the anterior cingulate cortex and motor cortex

**Authors: *C. L. BLOCK**[1], J. J. RAMIREZ[2], C. EROGLU[3], S. D. BILBO[4]
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**Abstract:** Prenatal air pollution (diesel exhaust particles; DEP) combined with maternal stress (MS) during the last trimester of gestation act synergistically on offspring to promote long lasting changes in neuroimmune function and deficits in communication and social behavior. Both changes in immune function and behavior are consistently more severe in males, in agreement with literature suggesting males are more vulnerable to immune activation early in life, resulting in increased vulnerability to neurodevelopmental diseases such as autism. Microglia are the primary immune cells in the CNS, they are important in immune host defense and are involved in the developmental pruning of synapses. Previous research has demonstrated that transgenic manipulation of microglia number or function alters synaptic development resulting in brain dysfunction. However, it is unclear whether environmentally relevant immune activation produces a similar phenotype. In this study, we aimed to determine whether prenatal DEP and MS (DEP/MS) alters microglia infiltration and cortical development in the anterior cingulate cortex and motor cortex, brain regions implicated in autism and social behavior. Mouse dams were intermittently exposed via oropharyngeal aspiration to DEP (50 μg × 6 doses) or vehicle (VEH) throughout gestation. This exposure was combined with standard housing for dams or nest material restriction (a model of maternal stress) during the last third of gestation. Prenatal DEP/MS altered social communication behavior in male offspring. At P15, prenatal DEP/MS resulted in changes in synapse number, microglial infiltration and neuronal distribution in cortical regions implicated in autism. Taken together, these results suggest that environmental

risk factors can alter microglia development/function, resulting in changes in brain development commonly seen in autism. This model thus affords a unique opportunity to explore environmentally relevant cellular and molecular mechanisms that contribute to neurodevelopmental disorders.

**Disclosures: C.L. Block:** None. **J.J. Ramirez:** None. **C. Eroglu:** None. **S.D. Bilbo:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.07/B50

**Topic:** A.07. Developmental Disorders

**Title:** The effects of maternal hyperglycemia on behavioral neurodevelopment in mice

**Authors: *S. HAIDERY**[1,2], L. THOMPSON[2], L. RUSSO[2], S. TRIMARCHI[2], J. BUSCINI[2], S. UGGIANO[2], S. GUARIGLIA[2]
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**Abstract:** Maternal health is crucial to neurodevelopment. Recent studies suggest that there is a correlation between gestational diabetes mellitus (GDM) and occurrence of Autism Spectrum Disorders (ASD). In GDM, human placental lactogen (HPL) and human placental growth hormone (HPGH) production promote hyperglycemia which remains persistent as a result of insufficient insulin production or insulin resistance. Although a pregravid body mass index (BMI) of 25 does increase the risk for GDM, it is not a prerequisite. To model the impacts of hyperglycemia without obesity on offspring neurodevelopment, we behaviorally phenotyped offspring of non-obese hyperglycemic dams. Dams were provided with glucose in their drinking water to induce gestational hyperglycemia. The male offspring of hyperglycemic dams (125-200 ug/dL) exhibited anxiety in open field test and elevated plus maze. These mice also harbored impairments in spatial learning in the Water-T-Maze test. Female offspring of hyperglycemic damn had greater obsessive compulsive tendencies in marble burying test, were less social in a social exploration test and showed a depressive tendency. Our data suggests that maternal hyperglycemia results in sex-specific behavioral changes in offspring that are relevant to ASDs and other developmental disabilities.

**Disclosures: S. Haidery:** None. **L. Thompson:** None. **L. Russo:** None. **S. Trimarchi:** None. **J. Buscini:** None. **S. Uggiano:** None. **S. Guariglia:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.08/B51

**Topic:** A.07. Developmental Disorders

**Support:** Nancy Lurie Marks Family Foundation

US Army Medical Research Acquisition/DOD

**Title:** Sex-bias in a mouse model of maternal antibody induced Autism Spectrum Disorder

**Authors: *A. GATA GARCIA**[1,2], A. PORAT[1], B. T. VOLPE[3], B. DIAMOND[1]
[1]Ctr. for Autoimmune and Musculoskeletal Dis., Feinstein Inst. for Med. Res., Manhasset, NY; [2]Hofstra Northwell Sch. of Med., Hempstead, NY; [3]Lab. of Functional Neuroanatomy, Feinstein Inst. For Med. Res., Manhasset, NY

**Abstract:** Autism Spectrum Disorder (ASD) consists of a range of neurodevelopmental conditions that disproportionately affect males in a 4 to 1 ratio and negatively impact everyday functioning beginning early in childhood. It is characterized by impairments in social interactions and communication, repetitive behaviors, and restricted interests or activities. Both incidence and prevalence of ASD have been markedly increasing over the past few decades, reaching 1 in every 68 children in 2010.
Factors in the *in-utero* environment alter neural development and therefore have been proposed to influence ASD susceptibility. One such risk factor is maternal brain reactive antibodies which penetrate the fetal brain after crossing the placenta and the immature blood brain barrier. We have developed a mouse model of maternal anti-brain antibody induced ASD using C6, an anti-brain antibody isolated from mothers of children with ASD. C6 targets Contactin Associated Protein-Like 2 (CASPR2), a protein expressed in neurons that has been implicated in ASD. C57Bl/6 fetuses (E15.5) exposed to C6 *in-utero* have a thinned cortical plate and a diminished population of progenitor cells in the ventricular zone. Furthermore, *in-utero* C6 exposure leads to ASD-like behaviors in adult mice. Interestingly, these neuroanatomical and behavioral phenotypes only affected males. Identifying the factors that contribute to these sex dependent effects of C6 could help us to understand the male bias in ASD.
In this study, we investigated the role of sex-chromosome and gonadal hormone differences in determining the susceptibility to C6. Specifically, we examined if susceptibility to the effects of C6 is increased by Y chromosome or male gonadal hormones, and decreased by the X chromosome or female gonadal hormones. We used the “Four Core Genotypes” mouse model, which allows for gonadal sex to be independent from sex chromosome complement, to isolate the genetic from the hormonal determinants of the sex-specific phenotypes. We analyzed DAPI stained sections from E15.5 fetuses exposed *in-utero* to C6 or to B1 isotype control for cortical

plate thickness. For this purpose, we developed a computer program that measures cortical plate and cortex areas, and calculates their ratio. The program was designed to increase objectivity and reproducibility of measurements. We found that higher levels of male hormones (represented by $XY^{-}$TgSry and XXTgSry gonadal males) and presence of the Y chromosome (represented by $XY^{-}$ gonadal female) significantly increased the susceptibility to develop a thinned cortical plate. Therefore, both gonadal hormones and sex chromosomes play a role in determining the susceptibility to C6.

**Disclosures:** **A. Gata Garcia:** None. **A. Porat:** None. **B.T. Volpe:** None. **B. Diamond:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.09/B52

**Topic:** A.07. Developmental Disorders

**Support:** Hussman Foundation Grant HIAS150001

**Title:** Altered dopaminergic markers in the basal ganglia in autism

**Authors: *K. SUBRAMANIAN**[1], J.-J. SOGHOMONIAN[2], C. BRANDENBURG[1], K. ZHANG[3], I. SULKAJ[3], B. RANDOLPH[3], G. J. BLATT[1]
[1]Neurosci., Hussman Inst. for Autism, Baltimore, MD; [2]Anat. and Neurobio., Boston Univ. Sch. of Med., Boston, MA; [3]Boston Univ., Boston, MA

**Abstract:** The main output for midbrain dopamine neurons is to the basal ganglia (BG). The BG are connected to the cerebral cortex and the cerebellum. Specific circuits within the BG are involved in motor and non-motor functions. Bilateral BG lesions lead to social communication challenges and/or repetitive behaviors. Specific lesions observed in such patients have remarkable similarity to behaviors observed in individuals with autism. A recent study on the prevalence of Parkinsonism found a significantly higher rate (20-27%) among individuals with autism compared to the general population (0.1%-0.9%), suggesting shared neurobiological origins and pathways. Since altered dopaminergic neurotransmission leads to classic Parkinson's symptoms, changes to the dopamine system within the BG in postmortem autism brain tissues was examined. Receptor autoradiography was used to measure dopamine type 1 (Drd1) and dopamine type 2 (Drd2) receptors in the caudate (CAU), putamen (PUT), nucleus accumbens (NAC) and subthalamic nucleus (STN). In situ hybridization histochemistry was utilized to measure mRNA levels of Drd2 receptors in the CAU and PUT. There was a significant increase in the density of Drd2 receptors in the NAC ($p=0.03$) and a trend towards significance in the STN ($p=0.0985$). In the striatum there was no significant change in the CAU ($p=0.2262$) or PUT ($p=0.1069$) individually. However, when taken together, CAU and PUT resulted in significantly

higher Drd2 receptor density values (p=0.0431). Also, significantly higher expression of Drd2 receptor mRNA was found in the CAU (p=0.00462) and the PUT (p=0.0483) of autism brains compared to age and sex-matched controls. In addition, no significant change between autism and controls for Drd1 receptor density was observed in any of the examined areas. In summary, the data suggests that specific regions of the BG in autism have significant increases in Drd2 receptor density and mRNA expression but not in Drd1. Since Drd2 is preferentially expressed in the indirect pathway of the BG and is considered to be important to inhibit unwanted actions, altered activation of Drd2 could act to dysregulate unintended actions contributing to stereotypy in autism. Taken together these data indicate a region-specific circuit specific change in the dopamine pathway in autism that could contribute to an excitatory/inhibitory (E/I) imbalance and increased risk for Parkinsonism. Future studies will aim to examine whether there are other neuromodulators whose expression is altered that may also impact the BG circuitry.

**Disclosures: K. Subramanian:** None. **J. Soghomonian:** None. **C. Brandenburg:** None. **K. Zhang:** None. **I. Sulkaj:** None. **B. Randolph:** None. **G.J. Blatt:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.10/B53

**Topic:** A.07. Developmental Disorders

**Support:** KAKENHI 25293124 (KF)

KAKENHI 24102505 (KF)

**Title:** Mitochondrial dysfunction and oxidative stress in rat brain prenatally exposed to valproic acid

**Authors: *K. MATSUO**, Y. YABUKI, K. FUKUNAGA
Dept. of Pharmacol., Tohoku Univ. Grad Sch. of Pharm Sci., Sendai/Miyagi, Japan

**Abstract:** Autism spectrum disorders (ASD) are a neurodevelopmental diseases characterized by social communication deficits and learning disability. Mitochondrial dysfunction and oxidative stress are strongly related to brain pathology in ASD. It is well known that prenatal exposure to valproic acid (VPA) increases a risk of pediatric ASD. We addressed a question whether autism-like behaviors in prenatally VPA-exposed rats (VPA rats) are associated with mitochondrial dysfunction and oxidative stress in brain. Prenatal VPA exposure (600 mg/kg, p.o.) at E12.5 was conducted and male rats were subjected to memory and social interaction tasks at 5-6 weeks of age. Prenatal VPA exposure elicited impairments in spatial reference memory, object recognition and social interaction. Enzymatic activities of mitochondrial electron transport chain complexes I

and II were decreased, while complex IV activity was elevated in hippocampus of VPA rats. These abnormal enzymatic activities were accompanied by reduced ATP production. The autism-like behaviors in VPA rats were improved by treatment with oxytocin (12 μg/kg, i.n.), which is a therapeutic neuropeptide improving social deficits in ASD patients. Interestingly, treatment with 5-aminolevulinic acid (ALA; 30 mg/kg, p.o.), which is a precursor of heme, restored impaired enzymatic activities of mitochondrial electron transport chain and reduced ATP production. ALA also suppressed elevated oxidative damage in hippocampus of VPA rats. Taken together, ALA ameliorates mitochondrial dysfunction and oxidative damage, thereby improving autism-like behaviors in VPA rats.

**Disclosures: K. Matsuo:** None. **Y. Yabuki:** None. **K. Fukunaga:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.11/B54

**Topic:** A.07. Developmental Disorders

**Title:** A novel role of S100B in neuronal trace metal homeostasis associated with dysregulation of autism-associated signaling pathways

**Authors: *S. HAGMEYER**[1,2], J. S. CRISTÓVÃO[3], T. M. BOECKERS[4], C. M. GOMES[3], A. M. GRABRUCKER[1,4]
[1]Univ. Limerick, Dept. of Biol. Scie, Limerick, Ireland; [2]Mol. Analysis of Synaptopathies, Neurol. Dept., Neurocenter of Ulm Univ., Ulm, Germany; [3]Biosystems and Integrative Sci. Inst., Univ. de Lisboa, Lisbon, Portugal; [4]Instiute for Anat. and Cell Biol., Ulm Univ., Ulm, Germany

**Abstract:** Several studies reporting elevated levels of the cytokine S100B in autism spectrum disorders (ASD) patients show an association between symptom severity and S100B levels. In addition, the gene encoding for S100B has been recently identified as an autism risk gene. However, the precise role of S100B in the development of ASD is still unknown. Structural analyses of S100B have shown that the protein harbors calcium and zinc binding sites. Thus, we hypothesize a role in regulating neuronal trace metals. Intriguingly, alterations in neuronal trace metals homeostasis have been repeatedly associated with ASD and this might provide a possible mechanism how S100B is implicated in the development of ASD. Therefore, we investigated whether S100B might affect neuronal trace metal levels using primary hippocampal neurons. Additionally, we evaluated whether the zinc-dependent postsynaptic SHANK proteins known involved in synapse formation, composition, and function and associated with ASD, are affected by S100B induced alterations in neuronal trace metals. We show that high S100B levels lead to significant changes in intracellular zinc levels of primary hippocampal neurons. These changes were abolished by the supplementation of zinc. Further, using a mutant of S100B with reduced

zinc binding capacity, we proof that the observed reduction of intracellular zinc levels indeed results from S100B´s zinc binding. Zinc levels, in contrast to calcium levels, were highly affected. By altering intracellular zinc levels, the exposure of neurons to S100B affects the ASD-associated SHANK protein concentration at synapses. Thus, taken together, our results represent a possible connection of different environmental factors (inflammation, trace metal dysregulation) that have been all reported to be involved in the development of ASD and point towards a combined action at glutamatergic synapses resulting in synaptic dysfunction

**Disclosures: S. Hagmeyer:** None. **J.S. Cristóvão:** None. **T.M. Boeckers:** None. **C.M. Gomes:** None. **A.M. Grabrucker:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.12/B55

**Topic:** A.07. Developmental Disorders

**Title:** Embryonic exposure to fluoxetine selectively reduces communication and increases anxiety in male mice while increasing repetitive behaviors in both sexes

**Authors: *M. P. LEUSSIS**, E. A. PETERSON, A. POWERS
Psychology Dept., Emmanuel Col., Boston, MA

**Abstract:** Genetic and environmental factors contribute to autism spectrum disorder (ASD), yet little is known about which environmental factors increase the risk for ASD. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy has increased in recent years. Epidemiological studies have linked SSRI use during pregnancy to a small but significant increase in risk of ASD. The specific long-term neurobiological consequences of prenatal SSRI exposure require further evaluation. This study examined the effects of prenatal exposure to fluoxetine in mice on behaviors relevant to ASD from neonatal development through adulthood. C57BL/6J dams were administered fluoxetine at 0.6 (low) or 6.0 (high) mg/kg/day or saline from embryonic days 8 to 18. Juvenile mice were tested in a developmental test battery that measured ultrasonic vocalizations and neuromotor reflex development. In adulthood, offspring were tested in a battery designed to examine changes in ASD-related social/communicative behaviors, repetitive behaviors, and anxiety behaviors. In juvenile mice, prenatal exposure to fluoxetine sex-dependently reduced the frequency of ultrasonic vocalizations in male mice. Fluoxetine did not detrimentally affect neuromotor development. Both adult males and females prenatally exposed to high, but not low, doses of fluoxetine exhibited an increase in repetitive behaviors in the marble burying task. However, males exposed to fluoxetine exhibited an increase in anxiety in the elevated plus maze, whereas females did not show any change in anxiety. Fluoxetine exposure did not affect behavior in the social preference test, self-grooming or passive

avoidance. Results suggest that males are more sensitive than females to disruptions in serotonin balance during prenatal development, producing long-term changes in behaviors including communication deficits, increased repetitive behaviors, and heightened anxiety. These findings highlight the need for more systematic studies to evaluate the impact of fluoxetine exposure during other periods of prenatal or early neonatal development.

**Disclosures:** **M.P. Leussis:** None. **E.A. Peterson:** None. **A. Powers:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

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**Program#/Poster#:** 462.13/B56

**Topic:** A.07. Developmental Disorders

**Support:** Oberlin College Grant-In-Aid

Oberlin College Research Fellowship

**Title:** Volatile organic chemical exposure affects general development and CNS cell type marker gene expression in zebrafish embryos

**Authors: *B. S. CARTER**, D. L. THOMAS, Y. Z. PRYOR, J. G. RUFFATTO
Neurosci., Oberlin Col., Oberlin, OH

**Abstract:** The role of environmental factors in neurodevelopment and Autism Spectrum Disorders (ASD) is not well characterized. Recent epidemiological findings suggest that exposure of pregnant mothers to volatile organic chemicals (VOCs) has a direct correlation with increased ASD prevalence in their children. However, there have been no studies to date to test how such chemicals impact brain development and if they regulate ASD-associated physiology. We investigated the impact of multiple VOCs (e.g. methylene chloride, trichloroethylene) on neurodevelopment in zebrafish embryos. Titration experiments defined phenotypic and lethal dosage for each chemical; gross morphological phenotypes were observed by brightfield microscopy, and gene expression of different CNS cell type markers were measured by qPCR. Initial results indicate VOCs can induce dose-dependent changes in overall development of zebrafish embryos and result in decreased CNS cell type marker expression for multiple neurotransmitter systems, including excitatory and inhibitory neurons. The character of these effects varies between specific VOCs. Our findings suggest that volatile organic chemicals can regulate neurodevelopment and likely do so through multiple mechanisms. Future experiments characterizing these mechanisms can inform appropriate usage of these chemicals and may add to knowledge of the molecular biology underlying ASD.

**Disclosures:** **B.S. Carter:** None. **D.L. Thomas:** None. **Y.Z. Pryor:** None. **J.G. Ruffatto:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.14/B57

**Topic:** A.07. Developmental Disorders

**Support:** Deanship of scientific research - The university of Jordan

**Title:** Comparison of irisin plasma levels in autistic patients to control in Jordan

**Authors:** *M. N. ALDAHABI[1], ***M. N. ALDAHABI**[1], Z. ALKAYED[3], L. ALZGHOUL[2], N. ABU TARBOUSH[2]
[1]Physiol. and Biochem. Dept., [2]Physiol. and Biochem. Dept. - Sch. of Med., Univ. of Jordan, Amman, Jordan; [3]Sch. of Med., Univ. of jordan, Amman, Jordan

**Abstract:** Irisin, the newly discovered myokine, is responsible for the formation of brite (brown in white) or beige adipocytes. Interestingly, Irisin was detected in the Purkinje cells of cerebellum, cerebrospinal fluid (CSF) and paraventricular neurons in hypothalamic region. Irisin has been proposed to play a role in neural cell differentiation, to be involved in dendritic spine formation, and to have a correlation with gene expression of brain-derived neurotrophic factor (BDNF) and homocysteine blood levels. Autism spectrum disorder (ASD) is a multifaceted neurodevelopmental disorder where genetic and environmental factors play a role in its development and pathogenesis. The arrest of neural development, with reduced dendritic spine density, and reduction and incursion in Purkinje cells are some of the neuropathological hallmarks of ASD. In addition, BDNF has been implicated in the pathogenesis of ASD and, recently, homocysteine has also been implicated as the main environmental factor in the pathogenesis of ASD. Given the aforementioned factors that have been demonstrated to be in relation to ASD and Irisin, and being not investigated before according to the authors' knowledge, we aimed to compare Irisin plasma levels in Jordanian children affected by ASD to their age and gender matching healthy controls. The quantitative measurements of Irisin in human plasma samples have been performed using commercial enzyme linked immunosorbent assay (ELISA) kit (EK-067-16, Phoenix Pharmaceuticals Inc., CA, USA), phonetics and EEG assessments have been obtained through medical reports. The preliminary findings of this study were: 1) Irisin level in ASD patients were significantly less compared to their control group. 2) Irisin level was decreased in ASD patients with abnormal EEG or those who are non-phonetic compared to other ASD patients; however it did not reach significance 3) There was no correlation of Irisin plasma level with age of ASD patients or controls.

**Disclosures:** **M.N. Aldahabi:** None. **Z. Alkayed:** None. **L. Alzghoul:** None. **N. Abu Tarboush:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.15/B58

**Topic:** A.07. Developmental Disorders

**Title:** A preliminary investigation on prenatal stress and associated risk factors for development of autism spectrum disorder

**Authors: *S. GOVINDARAJ**[1], P. KANAGASABAI[2], R. RAJAN[1]
[1]Physiol., Univ. of Madras, Chennai, India; [2]Holistic Solutions for Autism, Swabhimaan, Chennai, India

**Abstract: Background:** Stress is an inevitable part of human life, people begin to experience stress at early stages of life, even before birth. Prenatal stress has been linked to several diseases and disorders including many adverse neurobehavioral outcomes, which may share pathophysiology of autism. The severity depends on intensity, duration and time period of stress exposure. Autism Spectrum Disorder (ASD) is the heterogeneous neurodevelopmental disorder with unknown etiology and characterized by impairment in social interaction, communication deficits, restrictive and repetitive behavior. Generally, the incidence of ASD is more in male than female. At present globally it has been estimated the ratio of the ASD against normal children is 1 in 100-150, in the USA 1 in 88 children, in the UK 1 in 64 and in the South Korea 1 in 38.
**Objective:** The present study is to investigate the possible association of prenatal stress as a risk factor for the development of ASD in the offspring.
**Study design:** The questionnaire-based retrospective survey study was conducted and it consists of fifty mothers of children who has been already diagnosed with ASD aged between two to seven years and fifty mothers of children with no diagnosis of any kind of neurodevelopmental diseases aged between two to seven years. The ASD subjects were recruited from “Swabhimaan Holistic Solution for Autism”, is a special school for children with ASD. The data collection was done by distributing the questionnaires to the mothers of children with ASD. For control group, the data collection was done from “New Wisdom School” (Chennai, India).
**Result:** The study reveals that higher incidence of different sources of prenatal stress such as occupational stress, illness of family members, the estrangement of spouse and conflicts with family members were found in mothers’ of ASD children. The ASD group also showed a higher incidence of prematurity, birth complications, health problems, maternal illnesses, and advanced maternal age compared with the normal population. Additionally, people who were

experienced moderate and severe level of stressful experiences during first and second trimester showed severe autistic features.

**Disclosures: S. Govindaraj:** None. **P. Kanagasabai:** None. **R. Rajan:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.16/B59

**Topic:** A.07. Developmental Disorders

**Title:** Association of zinc deficiency with gastro-intestinal abnormalities in an Autism Spectrum Disorder mouse model

**Authors: *A. SAUER**[1], T. M. BOECKERS[1], A. M. GRABRUCKER[2]
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**Abstract:** Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by their core symptoms - delayed acquisition of speech, deficits in social interactions and stereotypic behaviors. Genetic factors might be responsible or facilitate the occurrence of ASD but in addition to a combination of ASD-related genes, specific environmental factors may act as risk factors triggering the development of ASD. A growing amount of research indicates that abnormalities in the gastrointestinal (GI) system during development might be a factor in ASD. Many patients with ASD have symptoms associated with GI disorders. We hypothesize that metal ion imbalances during pregnancy are linked to disturbances in the gastrointestinal (GI) tract and may be an important factor for the development of the ASD associated pathology. Zinc status influences and is influenced by multiple factors and an interdependence of prenatal and early life stress, immune system abnormalities, impaired GI functions, and zinc deficiency is hypothesized, linking several environmental factors discussed in ASD in a common proposed mechanism. Here, we show that maternal zinc deficiency leads to GI abnormalities in the offspring, triggering the impairment in metal absorption in the GI tract, but also mediating inflammatory responses. We show that maternal zinc deficiency causes alterations in the Microbiome of the offspring and alters specific inflammatory markers. The alterations in species of microbiota are similar to reported differences in humans with ASD. The inflammatory markers altered are also similar to the ones reported in human patients with ASD. Thus, we provide a link between several environmental factors in autism. Furthermore, to prevent the detected alterations, we characterize novel nutraceuticals that might overcome imbalances of dietary zinc absorption.

**Disclosures: A. Sauer:** None. **T.M. Boeckers:** None. **A.M. Grabrucker:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.17/B60

**Topic:** A.07. Developmental Disorders

**Title:** Elevated microglial populations in the cerebral cortex in autism spectrum disorders

**Authors: *M. S. MANIERKA**
Integrative Program in Neurosci., Univ. of Nevada Reno, Reno, NV

**Abstract:** Critical for both immune defense and synaptic development, microglia may play a key role in the etiology of autism spectrum disorders (ASD). These dynamic cells shift between several morphological states to fulfill a variety of functions, including synapse maintenance and pruning, and primary immune defense. Signs of increased inflammation in the brain and an excess number of immature synapses found in ASD may be the result of abnormal microglial function during development. Previous research has suggested an increase in microglial density in the prefrontal cortex of ASD patients. Given the broad spectrum of autism cognitive symptoms, it seems unlikely that any etiological factor could be restricted to a single cortical region. Instead, we predict that elevated microglial populations are a widespread feature of the ASD cortex.
To explore this possibility, we compared the cortical densities of two unique glial types: microglia and oligodendrocytes. Density counts were conducted in the supragranular layers (II and III) of posterior parietal cortex (Brodmann area 7) in six autistic and six neurotypical controls, and in the lateral/superior temporal cortex (Brodmann areas 21/22) in five autistic and three neurotypical controls. Tissue blocks were sectioned at 40µm across the cortical layers and stained with thionin to label Nissl bodies. To estimate cell population densities, counts were acquired from multiple tissue sections taken from each block using an optical dissector (Stereologer, SRC Inc.). In both parietal and temporal cortices, microglial densities were significantly increased in the ASD subjects. No difference in oligodendrocyte density was found between ASD and neurotypical groups. These findings support a persistent generalized increase in microglial density in the ASD cortex. The ‘distraction’ of an immune challenge during critical periods of synaptic development could prompt excess proliferation of microglia, as these cells attempt to fulfill both developmental and immunological functions in the ASD cortex. Given that this density increase is observed across tissue samples from adolescents and adults, the disruption to microglial populations is hypothesized to be a chronic cortical feature linked to ASD. Further work is needed to determine if microglial disturbances are correlated with other synaptic and cortical patterning changes associated with ASD.
2300 character limit

**Disclosures: M.S. Manierka:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.18/B61

**Topic:** A.07. Developmental Disorders

**Support:** NRF-2015R1D1A1A01059119

**Title:** Optogenetic stimulation of the basal forebrain parvalbumin neurons rectified excitation-inhibition imbalance in an animal model of autism

**Authors: J. H. LEE**[1], S. G. LEE[1], C. YEON[1], J. JUNG[1], J. LEE[1], *T. KIM[2]
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**Abstract:** Autism is a neurodevelopmental disorder with persistent deficits in social communication and social interaction, and restricted and repetitive patterns of behavior, interest, or activities, affecting 1-2.5% of all children. But the pathophysiology of autism is still poorly understood. Recently, increased excitation/inhibition ratio has been proposed as one of the characteristic pathophysiological mechanisms of autism. Deterioration of gamma band oscillations (GBO) was observed in children with autism spectrum disorders or in the animal model of autism. We reported that parvalbumin (PV) neurons in the basal forebrain (BF) play a key role in regulating GBO in the cerebral cortex by activating inhibitory interneurons in the cerebral cortex. Therefore, we hypothesized that the repeated stimulation of BF PV neurons might rectify the excitation/inhibition imbalance by increasing inhibitory neuronal activities in the cortex. First, we developed autism mouse model using intrauterine valproic acid exposure on embryonic day 10.5 of PV::Cre mice in which the expression of Cre recombinase is specifically controlled by PV expression. Secondly, when PV::Cre autism model mice were born, we injected viral vector (AAV5-DIO-ChR2-EYFP) into the basal forebrain, and implanted fiber optic cannula and electrodes for electrophysiological recordings after 2 weeks. After recovery, intermittent photostimulation at 40 Hz was given for 2 hours a day at the beginning of dark period, and repeated for one week. Before and after the one-week optogenetic stimulation, a series of behavioral assessments were to be carried out, including, but not limited to, three chamber test, nest building behavior, open field test, and novel object recognition test. Optogenetic GBO generation was also compared between before and after 1-week photostimulation period. Molecular markers for excitatory (PSD-95, vGluT1, alpha-CaMKII and synaptophysin) and inhibitory (GAD67, Reelin, and connexin 36) were measured in both treatment and non-treatment groups. The experiments are in progress and the results are pending. We are investigating whether E/I balance is restored in molecular markers and

electrophysiology, and consequently the behavioral abnormalities of autism mouse model is reduced by repeated photostimulation of BF PV neurons. We cautiously expect that effective activation of the inhibitory neural network in the cortex may have therapeutic implication in autism model mice.

**Disclosures:** **J.H. Lee:** None. **S.G. Lee:** None. **C. Yeon:** None. **J. Jung:** None. **J. Lee:** None. **T. Kim:** None.

**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.19/B62

**Topic:** A.07. Developmental Disorders

**Support:** Lurie Center for Autism

**Title:** Maternal immune activationwith a TLR7 agonist results in a distinct behavioral phenotype with relevanceto neurodevelopmental psychiatric disorders

**Authors:** J. O. ROBBINS[1], E. L. MOKLER[1], C. J. MCDOUGLE[2], G. MISSIG[1], ***W. A. CARLEZON, Jr**[1]
[1]Behavioral Genet. Lab., McLean Hospital, Harvard Med. Sch., Belmont, MA; [2]Lurie Ctr. for Autism, Lexington, MA

**Abstract:** Accumulating evidence suggests that maternal immune challenge during gestational and perinatal periods can have lasting effects on neurodevelopment. Previous work has demonstrated that the offspring of pregnant mice treated with immunoreactive agents can exhibit a behavioral phenotype with key features of autism spectrum disorder (ASD). This work is complemented by previous observations that some individuals with ASD exhibit atypical expression of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). Previous immune challenges have primarily employed agents (e.g., PolyI:C, lipopolysaccharide) that target subtypes 3 and 4 of the Toll-like receptor (TLR) family, a class of receptor proteins that regulates the innate immune response. The current study sought to manipulate TLR7, thereby expanding the repertoire of innate immune targets studied. In addition to its novelty as a target in maternal immune activation models of autism, TLR7 is highly expressed in the placenta, its expression is developmentally regulated in the brain during the perinatal period, and its activity has been implicated in the pathogenesis of systemic autoimmune disease and preeclampsia, both putative ASD risk factors. Activation of TLR-7 by its selective agonist, imiquimod (IMQ), represents a potentially novel approach with which to model immune-mediated ASD phenotypes in mice. Pregnant dams were administered 3 subcutaneous injections of the TLR-7 agonist or saline vehicle on embryonic day 12, 14, and 16, and the

offspring were subjected to a battery of ASD-relevant behavioral assays at various developmental time-points. Offspring of dams treated with IMQ exhibit a profound behavioral phenotype characterized by atypical patterns of ultrasonic vocalization, increased repetitive behaviors, reduced anxiety-like behavior, fragmented social behavior, and hyperactivity under some (but not all) testing conditions. Although there is some overlap between this phenotype and those observed in other maternal immune activation models used in the study of ASDs, it differs in several behavioral domains and therefore may enable new insights on immune involvement in other psychiatric disorders characterized by these signs.

**Disclosures: J.O. Robbins:** None. **E.L. Mokler:** None. **C.J. McDougle:** None. **G. Missig:** None. **W.A. Carlezon:** None.

**Poster**

**462. Autism: Environment and Pathology**

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**Topic:** A.07. Developmental Disorders

**Support:** National Natural Science Foundation of China #031500842

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Guangdong Natural Science Foundation 2016A030313082

**Title:** Impaired Purkinje neuron dendritic development and motor dysfunction in a VPA-induced mouse autism model

**Authors: R. WANG**, J. TAN, Y. ZHENG, *L. ZHANG
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**Abstract:** Autistic spectrum disorder (ASD) is now believed to be correlated with cerebellar developmental deficits by various transgenic mouse models. However, due to heterogeneity of ASD related genetic factors, single gene mutation may not cover the whole picture of ASD pathology in cerebellum. We thus employed maternal exposure of valproic acid (VPA) to generate a mouse ASD model, on which the post-natal development of cerebellar Purkinje cells (PCs) was investigated along with motor function. We found significantly reduced PCs number in most lobules of cerebellar cortex in adult VPA offspring mice. These mice also showed elevated apoptosis in neuron progenitor cells in cerebellar cortex. Golgi staining showed reduced dendritic branching complexity of PCs in VPA-treated mice. In consistent with those developmental disorders, those mice showed impaired motor coordination or motor learning functions on Rota-rod and a new LadderScan behavioral paradigm, in addition to impaired social preference and novelty. Further molecular studies showed that these abnormalities were

correlated with alternation in brain derived neurotropic factor (BDNF) -receptor tyrosine kinase B (TrkB) pathway. In summary, our study showed dendritic under-development in cerebellar Purkinje neurons and impaired motor function, both of which were accompanied with social deficits. These results further supported the involvement of cerebellar disorder in ASD pathology.

**Disclosures:** **R. Wang:** None. **J. Tan:** None. **Y. Zheng:** None. **L. Zhang:** None.

**Poster**

**462. Autism: Environment and Pathology**

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**Program#/Poster#:** 462.21/B64

**Topic:** A.07. Developmental Disorders

**Support:** Lurie Center for Autism

Teamsters Local 25 Autism Fund

**Title:** Sleep, epileptiform activity, and EEG metrics to assess immune mouse models of autism spectrum disorder (ASD)

**Authors: *G. MISSIG**[1], E. L. MOKLER[1], J. O. ROBBINS[1], A. J. ALEXANDER[1], C. J. MCDOUGLE[2], W. A. CARLEZON, Jr.[1]
[1]Behavioral Genet. Lab., McLean Hosp., Boston, MA; [2]Lurie Ctr. for Autism, MGH, Lexington, MA

**Abstract:** Increasing evidence suggests a role for inflammatory processes in autism spectrum disorders (ASDs). Some individuals with ASDs show elevated inflammatory markers and neuroimmune responses, as well as epidemiological association with familial autoimmune disorders. These findings raise the possibility that there is a subtype of ASD that is immunological in origin. Previous research in mice has shown that immune system activation during critical developmental periods can result in a phenotype that reproduces some of the core features of ASD. We have recently developed a “multiple hit” immune model, whereby mice are exposed to repeated perinatal immune insults. In this model, pregnant mice are injected with the viral mimic poly(I:C) (20 mg/kg) on gestational day 12.5 in accordance to an established model of maternal immune activation. A subset of these offspring receives a second injection of LPS (lipopolysaccharide) (10 mg/kg) to induce a robust innate immune response on postnatal day 9. We have previously found that this model leads to a state of persistent immune activation in offspring, which persists into adulthood, as well as a pronounced ASD-like behavioral phenotype with mice displaying deficits in social and communication-like behavior, increased repetitive behavior. Here, we examine the effect of this multiple hit immune activation model on two

physiological measures that are commonly dysregulated in individuals with ASD: sleep and electroencephalography (EEG) epileptiform activity. A wireless transmitter enabling continuous data collection was implanted at postnatal week 6 and measurements of EEG, electromyography (EMG), activity, and temperature were recorded for several weeks. Two time points were examined, one at 7 weeks of age and a second at 13 weeks to examine changes across development. There were marked changes in sleep patterns (increased slow-wave sleep) and changes in EEG spectral power that resembles those found in individuals with ASD. Considering that epilepsy is found in a higher percentage of individuals with ASD, we examined EEG recordings from perinatal immune-activated mice for the presence of epileptiform activity. Analysis revealed that a large proportion of the mice that received postnatal LPS displayed heightened levels of epileptiform activity (spike-wave discharge) during sleep. In sum, perinatal immune activation resulted in alterations in sleep and epileptiform activity resembling aspects of ASD, further supporting a potential immunological involvement in ASD and co-morbid seizure disorders.

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**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 462.22/B65

**Topic:** A.07. Developmental Disorders

**Support:** Deanship of Scientific Research - The University of Jordan

**Title:** Lower serum 25-hydroxycalciferol levels in autistics compared to healthy controls in Jordan

**Authors: *L. ALZGHOUL**[1], M. ODEH[2], O. ABU HANTASH[2], M. ALDAHABI[1], L. AL-EITAN[3]
[1]Dept. of Physiol. and Biochem., [2]Sch. of medicine, The Univ. of Jordan, Amman, Jordan; [3]Jordan Univ. of Sci. and Technol., Irbid, Jordan

**Abstract:** Autism spectrum disorder (ASD) is a neurodevelopmental disorder. It characterized by a socio-communicational impairment with restricted or repetitive interest and activity. In addition, sleep and GI disturbances as well as the decrease in bone density are also noticed in many patients with ASD. These defects, especially the one that related to the bone density, highlight the possible role of vitamin D in the development of ASD. In addition to its role in calcium homeostasis, studies suggested that vitamin D work as a neurosteroid hormone which plays a crucial role in brain development by its involvement in cell proliferation and

differentiation. Moreover, Vitamin D is suggested to play a role in brain detoxification. In addition, it also considered as a prohormone that exerts its functions through its active metabolites. Vitamin D is obtained from natural sources either from dietary vegetable as Vitamin $D_2$, also known as ergocalciferol, or as cholecalciferol D3 which obtained from animals or produced in the skin. Both $D_2$ and $D_3$ are biologically inert, and is subsequently converted in the liver to 25-hydroxyvitamin D (25[OH]D), which consist the major circulating form of vitamin D, and then in the kidney and other organs to 1,25-dihydroxyvitamin D, the active form of vitamin D. Recently, many studies highlighted the decreased level of (25[OH]D) in autistics. Moreover, Vitamin D supplement shows improvement in the behavior, IQ, sleep pattern and other symptoms associated with ASD. **Hence the aim of this study was to examine the association between 25[OH]D blood levels and autism in Jordan** To study that, serum total 25-hydroxycalciferol (25-OH-D) level was measured in 65 ASD patient and 70 age and gender matched healthy controls using LCMSMS. In addition Serum calcium levels were also measured using the automated standard laboratory method. Our data revealed 1) statistically significant lower levels of 25-OH-D in ASD group compared to controls, 2) and no significant difference was found in calcium levels. These data suggest a possible role of low vitamin D in the pathophysiology of ASD, yet its role is in a mechanism other than affecting calcium levels.

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**Poster**

**462. Autism: Environment and Pathology**

**Location:** Halls A-C

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**Program#/Poster#:** 462.23/C1

**Topic:** A.07. Developmental Disorders

**Support:** NICHD: HD081261

T32: AG021890

**Title:** Developmental exposure to Prozac combined with maternal tryptophan depletion sex dependently worsens social behavior in adolescent mice

**Authors: *V. GARBARINO**[1], M. T. EDWARDS[1], L. F. FERREIRA[2], T. SANTOS[1], M. A. JAVORS[1], L. C. DAWS[3], G. G. GOULD[2]
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**Abstract:** Depression is a serious mood disorder that may require antidepressant use during pregnancy. Safety concerns have been raised about the effects of selective-serotonin reuptake

inhibiting (SSRI) antidepressants on fetal brain development and their potential to increase the risk of autism in developmentally exposed offspring. The most commonly prescribed SSRI for use during pregnancy is fluoxetine (Prozac). Fluoxetine blocks serotonin (5-HT) reuptake by the 5-HT transporter. 5-HT is vital for shaping neural circuitry during development, and aberrant fetal 5-HT levels can increase the risk of autism, which is diagnosed based on the dual manifestation of social behavior deficits and repetitive behaviors. Fetal 5-HT availability may be highly dependent upon maternal availability of its precursor, tryptophan (TRP), hence, elucidation of the relationship between maternal and fetal TRP and 5-HT demand and availability is crucial to understanding their role in autism susceptibility. Using a mouse model of maternal SSRI exposure with dietary TRP manipulations during pregnancy and lactation, we measured the social interaction and novelty preference, as well as repetitive behavior of adolescent offspring. In recent studies we demonstrated that a daily sub-therapeutic dose (1 mg/kg) of fluoxetine, or a maternal dietary TRP depletion, is able to impair offspring sociability with sexually dimorphic relevance to hallmark autistic behaviors. Exposed males demonstrated worsened social behavior outcomes, while exposed females tended to be more impacted in repetitive behavior measures. Our early results suggest that males may be more sensitive to in utero exposure to 5-HT altering factors, and that males and females may compensate for their developmentally altering effects by different mechanisms. We hypothesize that a clinically relevant dose (10 mg/kg) of fluoxetine will lead to severe behavioral impairments compared to controls, and that TRP depletion will compound these outcomes, but may be rescued with the addition of a TRP enhanced maternal diet. We also anticipate finding higher levels of 5-HT turnover in fluoxetine exposed offspring brain tissue, and impairments in serotonergic neurodevelopment in offspring exposed to these 5-HT depleting manipulations. We aim to demonstrate if a maternal therapeutic dose of SSRI is able to cause developmental serotonergic system impairments that could cause persistent sociability and repetitive behavior deficits that might help to explain the increased incidence of autism in offspring who were developmentally exposed to SSRI's.

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**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.01/C2

**Topic:** A.07. Developmental Disorders

**Support:** JSPS KAKENHI Grant 23590124

AMED grant 15ek0109040h0002

**Title:** Implication of MUNC18-1-gene abnormalities in neurodevelopmental disorders

**Authors: *K.-I. NAGATA**, N. HAMADA, H. TABATA
Inst. For Developmental Research, Aichi Human Service Ctr., Kasugai, Japan

**Abstract:** While Munc18-1 is essential for presynaptic vesicle fusion in developed neurons, this molecule is likely to be involved in brain development since gene abnormalities in *MUNC18-1* (*STXBP1*) cause early infantile epileptic encephalopathy with suppression-burst (Ohtahara syndrome), neonatal epileptic encephalopathy and other neurodevelopmental disorders. We analyzed physiological and pathophysiological relevance of Munc18-1 during the cortical development. Munc18-1-knockdown impaired cortical neuron positioning during mouse corticogenesis. Time-lapse imaging revealed that the mispositioning was attributable to defects in radial migration in the intermediate zone and cortical plate. Munc18-1-binding protein, Syntaxin1A, was also critical for radial migration downstream of Munc18-1. As for the underlying mechanism, Munc18-1-knockdown in cortical neurons hampered post-Golgi vesicle trafficking and subsequent vesicle fusion at the plasma membrane *in vivo* and *in vitro*, respectively. Notably, Syntaxin1A-silencing did not affect the post-Golgi vesicle trafficking. These data indicate that Munc18-1 may regulate radial migration by modulating not only vesicle fusion at the plasma membrane to distribute various proteins to the cell surface but also preceding vesicle transport from Golgi to the plasma membrane. Although knockdown experiments suggests that Syntaxin1A does not participate in the post-Golgi vesicle trafficking, it was supposed to regulate subsequent vesicle fusion under the control of Munc18-1. Taken together, functional abnormalities of MUNC18-1 may induce aberrant cortical neuron migration leading to functional defects of cerebral cortex, and consequently contribute to the pathophysiologies of infantile epilepsies and other neurodevelopmental disorders with MUNC18-1 abnormalities.

**Disclosures:** **K. Nagata:** None. **N. Hamada:** None. **H. Tabata:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

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**Topic:** A.07. Developmental Disorders

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Shriners Hospital for Children 86500-NCA, 85220-NCA and 85300-NCA

Shriners Hospital for Children Postdoctoral Fellowship to OAB

**Title:** Folate receptor 1 is necessary for neural plate cell apical constriction during neural tube formation

**Authors: O. A. BALASHOVA**[1], O. VISINA[2], *L. N. BORODINSKY[3]
[1]Physiol. & Membrane Biol. - Shriners Hosp. for Children, [2]Shriners Hosp. for Children - Physiol. & Membrane Biol., [3]Univ. of California Davis, Sacramento, CA

**Abstract:** Folate supplementation prevents up to 70% of neural tube defects (NTDs), which result from a failure of neural tube closure during embryogenesis. The elucidation of the mechanisms underlying folate action has been challenging. Our study introduces *Xenopus laevis* as a model to determine the cellular and molecular mechanisms involved in folate action during neural tube formation.
We find that knockdown of folate receptor 1 (FOLR1) impairs neural tube formation and leads to NTDs. FOLR1 knockdown in neural plate cells only is sufficient to induce NTDs. FOLR1-deficient neural plate cells fail to constrict, resulting in widening of the neural plate midline and defective neural tube closure. Our results demonstrate that FOLR1 interacts with the adherens junction component C-cadherin and its molecular partner β-catenin. We find that neural plate cells undergoing apical constriction contain C-cadherin-immunopositive puncta associated with early endosomes, which suggests that C-cadherin endocytosis is involved in reduction of the apical surface in constricting cells. FOLR1 knockdown in the medial neural plate is accompanied by a decrease in the number of C-cadherin-containing endosomes in superficial cells. In addition, FOLR1 interacts with the insulin-like growth factor 1 receptor (IGF1R) and incubation of neurulating embryos with folinic acid leads to an increase in calcium transients in the neural plate and Akt activation. Moreover, FOLR1 knockdown results in a decrease in spontaneous calcium transients in the neural plate.
Altogether, these results support a model in which folate binding to FOLR1 triggers a specific signaling pathway that regulates cell adhesion and cytoskeletal dynamics essential for the formation of the neural tube.

**Disclosures: O.A. Balashova:** None. **O. Visina:** None. **L.N. Borodinsky:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

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**Program#/Poster#:** 463.03/C4

**Topic:** A.07. Developmental Disorders

**Support:** Ministry of Health, Labor and Welfare of Japan Research on Rare and Intractable Diseases Grant 24-078

JSPS grant-in-aid for Challenging Exploratory Research 25670486

JSPS grant-in-aid for Scientific Research (B) 24390270

**Title:** IGFBP3 deficiency leads to behavior impairment with monoaminergic dysfunction

**Authors: *M. ITOH**[1], H. DAI[2]
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**Abstract:** Insulin-like growth factor binding protein-3 (IGFBP3) regulates IGF bioactivity, induces apoptosis and inhibits cell growth independent of IGFs, but the functional role of IGFBP3 in the brain is not clear. In the present study, we revealed the effect of IGFBP3 on the brain by characterizing the phenotype of *igfbp3*-null mice. Compared to wild-type mice, *igfbp3*-null mice showed significantly decreased IGF-1 content in the brain but showed no change in weights of brain and body. In *igfbp3*-null mice the number of dendritic spines was significantly reduced, and the dendritic diameter was thin. In addition, in *igfbp3*-null mice, a decrease in phosphorylated Akt and ERK1/2 significantly reduced PSD-95 expression, and GAD65/67 expression was significantly decreased. These results indicate that IGFBP3 deficiency impairs neuronal structure and signaling. In behavioral studies, *igfbp3*-null mice were hyperactive, and a Y-maze alternation test revealed impaired spatial working memory, but no anxiety-like behavior. Monoaminergic analysis using HPLC indicated that *igfbp3*-null mice showed lower levels of dopamine and serotonin compared to wild-type mice, suggesting an abnormal monoaminergic neurotransmission. In conclusion, our studies demonstrated that the deletion of IGFBP3 results in behavioral impairments that are associated with abnormal synaptic function and monoaminergic neurotransmission, which helps to characterize the critical role of IGFBP3 in the brain.

**Disclosures: M. Itoh:** None. **H. Dai:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

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**Topic:** A.07. Developmental Disorders

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NIH grant R00NS080911

**Title:** Conditional Dnmt3a deletion in cortical pyramidal neurons alters DNA methylation and gene expression in mouse frontal cortex and hippocampus

**Authors: *E. A. MUKAMEL**[1], J. LI[2], C. LUO[3], R. CASTANON[4], J. R. NERY[4], J. LUCERO[4], K. UM[5], J. R. ECKER[6,7], M. BEHRENS[8]
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**Abstract:** DNA methylation is an essential epigenetic modification with a key role in brain development and synaptic plasticity. In mammalian genomes, DNA methylation typically occurs at cytosines in a CG-dinucleotide context (mCG), whereas substantial non-CG methylation (denoted mCH) is a unique feature of the epigenomes of neurons and, to a lesser extent, glial cells. Our earlier re-sults showed that mCH accumulates in brain during post-natal development, in parallel with syn-aptogenesis and neuronal maturation. The de novo DNA methyltransferase Dnmt3a is highly expressed in brain at this time, suggesting mCH accumulation in neurons may require precise regulation of Dnmt3a activity.
To test this hypothesis, we used isolation of nuclei tagged in specific cell types (INTACT). We produced a mouse carrying the INTACT construct and expressing Cre driven by the NeuroD6 promoter to establish a conditional Dnmt3a knockout (KO) mouse. In this mouse, Dnmt3a deletion from cortical and hippocampal pyramidal neurons occurs during the mid-embryonic phase, around embryonic day 13-15. Using the INTACT nuclear envelope tag, we isolated py-ramidal nuclei from frontal cortex and hippocampus from animals at postnatal day 39 to profile DNA methylation and transcription using MethylC-seq and RNA-seq, respectively. Compared to control animals, mCH was eliminated in pyramidal neurons from Dnmt3a KO animals in both brain regions, supporting the role of Dnmt3a in postnatal mCH accumulation. Global mCG levels in the Dnmt3a-KO animals were 10% lower in KO, and we identified hun-dreds of thousands differentially methylated regions (DMRs) with lower mCG in KO compared with controls. RNA-seq data from matched tissue samples displayed altered transcriptional ex-pression at hundreds of genes in the KO samples, with more pronounced changes in frontal cor-tex than hippocampus. In contrast with the largely unidirectional shifts in methylation levels, gene expression changes in the KO were balanced with similar numbers of up- and down-regulated genes. These results indicate that Dnmt3a is required for the non-CG methylation ac-cumulation in mouse brain. Dnmt3a alters both CG and non-CG methylation post-natally and is essential for the dynamic balance of the gene regulatory network during neuronal development.

**Disclosures: E.A. Mukamel:** None. **J. Li:** None. **C. Luo:** None. **R. Castanon:** None. **J.R. Nery:** None. **J. Lucero:** None. **K. Um:** None. **J.R. Ecker:** None. **M. Behrens:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.05/C6

**Topic:** A.07. Developmental Disorders

**Support:** Hope for Depression Research Foundation

NIH/NINDS R00NS080911

NIMH T32 MH020002-16A

**Title:** Environmental enrichment differentially influences transcription and epigenetic regulation in mouse dorsal vs. ventral dentate gyrus

**Authors: *C. L. KEOWN**[1], J. LI[1], X. WEN[2,3], N. O'TOOLE[2,3], U. BHATTACHARYYA[1], C. ANACKER[2,3], J. DIORIO[2,3], M. J. MEANEY[2,4], E. A. MUKAMEL[1], T.-Y. ZHANG[2,3]
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**Abstract:** Early life experience influences stress reactivity and mental health through effects on cognitive-emotional functions that are, in part, linked to gene expression pattern in the dorsal and ventral hippocampus. The hippocampal dentate gyrus (DG) is a major site for experience-dependent plasticity that associates with sustained effects on transcriptional activity, potentially mediated via epigenetic modifications including DNA methylation. We used whole genome bisulfite sequencing and Tet-assisted bisulfite sequencing (TAB-Seq) to profile DNA methylation and hydroxymethylation, respectively, in the DG of mice raised in standard housing (SH) and enriched environment (EE). These data were integrated with transcriptome (RNA-Seq) information from the same tissue. Because of the substantial molecular, functional and connectivity differences between the dorsal and ventral poles of the DG (dDG and vDG, respectively), we separately dissected these regions to examine their responses to EE.
Dorsal and ventral poles of the DG showed remarkable diversity in gene expression, with significant differential expression of 53% of all genes that are expressed in either region. Among the DE genes, a similar number of genes were upregulated in the dorsal and the ventral regions. We identified 152 genes differentially expressed in EE compared to SH in the dDG and 72 in vDG, including activity regulated immediate early genes *Fos*, *Egr2* and *Npas4*. Next, we identified over 10,000 differentially methylated regions (DMRs) between dDG and vDG in SH samples. Animals raised in EE showed nearly 60% more DMRs, suggesting that experience may support the molecular differentiation of the dorsal and ventral DG. Our results show that despite

consisting primarily of dentate granule cells, the dDG and vDG show substantial molecular diversity that may be supported by underlying differences in DNA methylation.

**Disclosures: C.L. Keown:** None. **J. Li:** None. **X. Wen:** None. **N. O'Toole:** None. **U. Bhattacharyya:** None. **C. Anacker:** None. **J. Diorio:** None. **M.J. Meaney:** None. **E.A. Mukamel:** None. **T. Zhang:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.06/C7

**Topic:** A.07. Developmental Disorders

**Support:** MH112763

MH094670

Howard Hughes Medical Institute

**Title:** Phenotypic characterization of a pyramidal-cell specific de novo methyltransferase Dnmt3a knock out mouse

**Authors: *A. PINTO-DUARTE**[1,3], J. LI[4], C. LUO[2,7], B. BUI[1], T. J. SEJNOWSKI[1,5,7], S. B. POWELL[6], E. MUKAMEL[4], J. R. ECKER[2,7], M. BEHRENS[1]
[1]CNL-S, [2]Genomic Analysis Lab., The Salk Inst. For Biol. Studies, La Jolla, CA; [3]Inst. for Neural Computation, [4]Dep. of Cognitive Sci., [5]Div. of Biol. Sci., [6]Dept. of Psychiatry, UCSD, La Jolla, CA; [7]Howard Hughes Med. Inst., La Jolla, CA

**Abstract:** DNA methylation is an epigenetic mechanism fundamental for establishing and maintaining cellular phenotypes throughout the lifespan of an individual. While occurring mainly in a cytosine-guanine (CG)-dinucleotide context, brain tissue also contains a substantial amount of non-CG methylation (mCH), whose accumulation coincides with transcriptional changes during synaptogenesis and neuronal maturation. The de novo DNA methyltransferase Dnmt3a is highly expressed in the brain during that period, and our preliminary in vivo and in vitro data suggest that this enzyme is responsible for the accumulation of mCH during the second postnatal week. Now, we have created a conditional Dnmt3a knockout mouse in which Dnmt3a deletion from pyramidal neurons occurs during late embryonic stage (around embryonic day E15, Neurod6-Cre). Gene ontology analysis of RNA-seq data from pyramidal neurons in the prefrontal cortex of our mouse revealed that the class of genes controlling neural excitability and synaptic functions was significantly downregulated, suggesting a likely role in information transmission. In preliminary behavioral experiments, we found our mouse to be viable, fertile and devoid of motor deficits, which contrasts with reports showing that animals with an earlier

Dnmt3a embryonic deletion (~E9, Nestin-Cre) underperformed on tests of neuromuscular function and motor coordination. Results from further behavioral testing, electrophysiological experiments and morphological analysis, which are currently underway, will help clarify the role of Dnmt3a in brain function.

**Disclosures:** **A. Pinto-Duarte:** None. **J. Li:** None. **C. Luo:** None. **B. Bui:** None. **T.J. Sejnowski:** None. **S.B. Powell:** None. **E. Mukamel:** None. **J.R. Ecker:** None. **M. Behrens:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.07/C8

**Topic:** A.07. Developmental Disorders

**Support:** NIH grant ES021534

**Title:** Sex and brain-region specific influences of prenatal stress and lead exposure on permissive and repressive post-translational histone modifications from embryonic development through adulthood

**Authors: *G. VARMA**[1], M. SOBOLEWSKI[2], D. ANDERSON[1], D. CORY-SLECHTA[2], J. SCHNEIDER[1]
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**Abstract:** Developmental exposure to prenatal stress (PS) as well as the neurotoxicant lead (Pb) can affect brain development and adversely influence behavior and cognition potentially through influences on the epigenome. Epigenetic gene regulation is crucial for normal brain development and misregulation in any form can result in neurodevelopmental disorders. Post-translational histone modifications (PTHMs) are an integral and dynamic component of the epigenetic machinery involved in gene regulation and the influence of PS and Pb exposures on PTHMs, from early developmental stages to adulthood, has not been studied. Here we examined the effects of Pb±PS on global levels of activating marks H3K9ac and H3K4me3 and repressive marks H3K9me2 and H3K27me3 in mouse hippocampus (HIPP) and frontal cortex (FC) at different developmental stages: E18, PND0, PND6 and PND60. Dams were exposed to 0 or 100ppm Pb before breeding followed by no PS (NS) or PS resulting in four treatment groups: 0-NS (control), 0-PS, 100-NS and 100-PS. Global levels of PTHMs varied from E18 through adulthood in control mice and were influenced by sex and brain-region. The normal developmental trajectory of PTHM levels was further modified by Pb±PS in a sex-, brain region- and age-dependent manner. Females appeared to show a preferential response to Pb alone in FC

and differentially to PS alone and combined Pb+PS in HIPP. In males, PS-induced increases were seen in FC, whereas PS produced reductions in HIPP; Pb-related increases occurred in both regions. Pb±PS-based changes continued to be observed in adulthood (PND60), demonstrating the lasting effect of these early life environmental events on these histone marks. These results add to our understanding of the epigenetic consequences of developmental Pb and PS exposures and support the need for additional studies to understand the functional significance of changes in PTHM levels on expression of individual genes and functional pathways.

**Disclosures: G. Varma:** None. **M. Sobolewski:** None. **D. Anderson:** None. **D. Cory-Slechta:** None. **J. Schneider:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.08/C9

**Topic:** A.07. Developmental Disorders

**Title:** Investigating the role of the schizophrenia risk gene ZNF804A in early brain development

**Authors: *Y. ZHOU**, F. DONG, Y. MAO
Biol., Penn State Univ., State College, PA

**Abstract:** ZNF804a was the first gene to reach genome-wide significance for psychosis when SNP rs1344706 was shown to be significantly associated combining SZ and bipolar disorder diagnoses. Several follow up genome-wide associated studies (GWAS) have replicated the association of rs1344706 with SZ and other psychosis in different populations. Although the association with SZ has been reported since 2008, the molecular function of ZNF804a remains unclear. We found that ZNF804a expression is high in the embryonic brain but decreased in the adulthood and ZNF804a localizes in both nucleus and dendrites. We performed in utero electroporation using B6 wild type mice on embryonic day 15 (E15) and transfected the neuronal progenitor cells with ZNF804a overexpression (OE) and knockdown (KD) constructs, both were tagged with GFP. On E18, the electroporated embryos were collected and the brains were processed with cryo-sectioning and fluorescent immunocytochemistry (ICC) staining. Quantitated results of GFP positive neuron showed overexpressing ZNF804a in utero significantly increased the migration of new born neuron, while knockdown endogenous ZNF804a significantly decreased the neuronal migration. To determine how ZNF804a regulates neuronal migration, we conducted the yeast two hybrid screen and identified novel proteins that interact with ZNF804a. Taken together, our study paved the road of understanding the molecular mechanism of ZNF804a and demonstrated its significant role for major mental illness in neuronal development.

**Disclosures:** **Y. Zhou:** None. **F. Dong:** None. **Y. Mao:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.09/C10

**Topic:** A.07. Developmental Disorders

**Support:** R21 NS101151-01

**Title:** *In vivo* assessment of infection route and vulnerability of neural progenitors to Zika virus

**Authors: *S. M. SHELTON**[1], K. N. PETERS[2], A. R. SOUCY[2], J. H. CONNOR[2], T. F. HAYDAR[1]
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**Abstract:** The rapid spread of Zika virus (ZIKV) and its association with abnormal brain development constitute a global health emergency. Congenital ZIKV infection produces a range of mild to severe pathologies, including microcephaly. These pathologies are specific to fetal brain tissue, where neural stem cells are targeted. To understand the pathophysiology of ZIKV infection, we use an *in vivo* mouse model of fetal brain development that recapitulates the human cytoarchitecture of early to mid-gestation. ZIKV PRVABC59, isolated from the blood of a patient in Puerto Rico in December 2015, is used to characterize ZIKV infection of neural progenitors and resulting changes in mouse brain development. Multiple dose concentrations, routes of administration, and inoculation periods are investigated at several points during gestation to characterize the development of congenital Zika syndrome. The targeted neural precursor types are identified at various stages of brain development using in utero electroporation. Changes in neuronal proliferation and migration are then quantified to inform the etiology of microcephaly. ZIKV injections with concurrent use of in utero electroporation allow for labeling of neural progenitor subtypes and identification of lineages susceptible to infection and transmission of ZIKV. Immunohistochemistry enables co-labeling of ZIKV positive cells and electroporated cells to determine cell-type specific infection by the virus in the developing brain. Infection of embryos allows for the study of developing mice and also cross-transmission between infected fetuses and the maternal circulation. This model provides a platform for robust *in vivo* screens of potential pharmacotherapeutics designed to limit ZIKV transmission and promote healthy development in infected fetuses that are also safe during pregnancy. Together, ZIKV infections in mothers and in developing mice at varying doses, inoculations, and stage in development combined with cell type specific in utero electroporation techniques will further elucidate the etiology of congenital Zika syndrome and microcephaly in an *in vivo* model of mammalian development.

**Disclosures:** **S.M. Shelton:** None. **K.N. Peters:** None. **A.R. Soucy:** None. **J.H. Connor:** None. **T.F. Haydar:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.10/C11

**Topic:** A.07. Developmental Disorders

**Support:** NCTR/FDA

**Title:** Identifying potential biomarkers and mechanisms associated with anesthetic-induced neurotoxicity in nonhuman primate

**Authors: *C. WANG**[1], C. WANG[3], X. HAN[3], F. LIU[1], Q. GU[1], S. LIU[1], T. A. PATTERSON[1], M. G. PAULE[1], J. P. HANIG[4], W. SLIKKER, Jr.[2]
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**Abstract:** It has been reported that the commonly used general anesthetics such as sevoflurane induce neurotoxicity in developing brains. However, there has been limited research evaluating whether and how anesthetic agents affect bio-lipids, the most abundant components of the brain other than water. Thus, assessing lipid profiles, especially from blood samples, may assist in the early detection of the neurotoxic effects that can be associated with general anesthesia.
Postnatal day (PND) 5 or 6 monkeys were randomly assigned to control (room-air; n=4) and sevoflurane-exposed (n=4) groups. Sevoflurane was delivered using an agent-specific vaporizer for 9 hours at a clinically-relevant concentration of 2.5%. Blood samples were collected at 0, 2, 4, 8 and 9 h during exposure in both the control and sevoflurane-exposed groups. Lipid extractions and analyses were performed using a mass spectrometer. 4-h after completion of anesthetic exposures, frontal cortical tissue was collected for histochemical and Western blot analyses.
Serum lipidomic analysis demonstrated that the levels of critical lipid components including acylcarnitines, phosphatidylcholines (PC) and phosphatidylethanolamines (PE) were significantly decreased during prolonged exposure to sevoflurane. In contrast, the amounts of triglyceride (TAG) and 4-hydroxynonenal were increased to abnormally high levels in sevoflurane-exposed monkeys. Consistently, histochemical staining and Western blot analyses of Bax protein revealed increased neuronal apoptotic damage after sevoflurane exposure.
These data suggest that prolonged exposure of neonatal monkeys to a clinically-relavent concentration of sevoflurane resulted in significant changes in lipid metabolism and subsequently, neuronal apoptotic damage. Monitoring specific lipid changes may provide

insights into the molecular mechanism(s) underlying general anesthetic-induced neurotoxicity and serve as sensitive biomarkers for the early detection of anesthetic-induced neuronal damage. Supported by NCTR /FDA

**Disclosures:** **C. Wang:** None. **C. Wang:** None. **X. Han:** None. **F. Liu:** None. **Q. Gu:** None. **S. Liu:** None. **T.A. Patterson:** None. **M.G. Paule:** None. **J.P. Hanig:** None. **W. Slikker:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.11/C12

**Topic:** A.07. Developmental Disorders

**Support:** MEXT 16H06530

**Title:** Paternal aging-induced DNA methylation in sperm: Possible effect on gene expression and behavior in offspring

**Authors: *N. OSUMI**[1,2], K. YOSHIZAKI[1], R. KIMURA[1], T. KOIKE[3], S. OKI[4], T. KIKKAWA[1], H. INADA[1], K. MOCHIZUKI[1], T. KONO[3,2], Y. MATSUI[5,2]
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**Abstract:** During these decades, neurodevelopmental diseases such as autism spectrum disorder (ASD) have been increased dramatically. Part of the reason can be parental aging caused by the rise of marriage age. Human epidemiological studies have repeatedly indicated that advanced paternal age, rather than maternal one, increases risk for ASD. Thus we have established a mouse model to challenge the underlying molecular mechanism for transgenerational epigenetic inheritance from sperm to offspring. We confirmed that advanced paternal age impaired vocal communication in their F1 pups and affected sensorimotor gating and spatial learning in adult. These phenotypes in F1 were rescued in F2 offspring when they were derived from young F1 father, suggesting epigenetic changes in sperm rather than increase of genetic mutation. Comprehensive DNA methylome analyses further revealed drastic changes in aged sperm, i.e., 96 hypomethylated and 16 hypermethylated genome loci, including NRSF/REST repressor motif in common. NRSF/REST was also identified from “transcription factor enrichment analyses”. We also found several schizophrenia/autism related genes in hypomethylated loci but not in hypermethylated ones. We are now struggling to obtain gene expression data for drawing a possible scenario how specific hypomethylated genome loci may result in disreguration of various genes related with neural development.

**Disclosures:** **N. Osumi:** None. **K. Yoshizaki:** None. **R. Kimura:** None. **T. Koike:** None. **S. Oki:** None. **T. Kikkawa:** None. **H. Inada:** None. **K. Mochizuki:** None. **T. Kono:** None. **Y. Matsui:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.12/C13

**Topic:** A.07. Developmental Disorders

**Support:** NIH/NICHD Grant HD087101

NIH/NICHD Grant HD004612

**Title:** Early developmental childhood leukodystrophy study via gene editing

**Authors: S. KUMAR**[1], C. SHIEH[2], N. SUWANNA[4], R. MATALON[5], *J. DE VELLIS[3]
[1]Semel Inst. for Neurosci-IDDRC, [3]Semel Inst. For Neurosci., [2]UCLA, Los Angeles, CA; [4]Mahidol Univ., Nakhonpathom, Thailand; [5]UTMB Children's Hosp., Galveston, TX

**Abstract:** Identified nearly a century ago, Canavan Disease (CD) is a fatal progressive childhood Leukodystrophy. It has not been curable due to the lack of understanding the early mechanisms of disease onset and its progression. First detected in Jewish decedents, now identified throughout the world within diverse ethnic background. CD is a result of mutation in Aspartoacylase (Aspa/ACY2) gene expressed in oligodendrocytes (OLs) in the brain. Presently 65 confirmed Aspa gene mutations has been identified with varied severity ranging from mild cognitive loss as in Autism, to severe spongy white matter and early death. The Aspa enzyme metabolizes N-acetylaspartate (NAA) to provide acetyl-CoA, thought to be the major source for lipid synthesis used for myelin formation, and ATP production in mitochondria. In the absence of Aspa enzyme, NAA level increases progressively in plasma and urine, which is detectable in affected infants. In CD infants, however, acetate therapy was not effective when tried after the onset of disease symptoms. Working with animal models of CD, our lab and others have contributed to the understanding of disease severity. We had also reported death of OLs, astrocytes and neurons in the brain. In our recent studies, we focused on early developmental gene expression by Gene Array and Metabolomics studies at P10, P20, from the onset to the peak stage of myelination in a mouse model of CD. The results presented expression profiles of multiple significant target genes resulting in alteration of structural and metabolic pathways. Our gene and protein analysis further validated impairment of these up- and down-regulated genes and altered pathways in ASPA mutants, suggesting possibility of other direct or indirect role of ASPA in CNS health and disease. In a therapeutic approach, we performed Aspa gene editing via homologous recombination using donor DNA and zinc finger nuclease (Zfn) technology in

newborn Aspa KO mouse neural cells. ASPA locus was targeted for gene editing to integrate the correct copy of the Aspa gene followed by termination codon to stop expression of the mutated gene. In addition, we have generated another cell line by integrating full Aspa gene at the safe harbor site using Rosa26-Zfn away from the Aspa gene mutation site within the same cell. Working with WT, KO and two above described edited cells, we have now validated molecular changes by gene expression analysis. The results also verified the fact that our Gene Trap method used to generate mutant mice strain does not contribute towards identified altered genes, hence are relevant to CD pathology.

**Disclosures: S. Kumar:** None. **C. Shieh:** None. **N. Suwanna:** None. **R. Matalon:** None. **J. De Vellis:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.13/C14

**Topic:** A.07. Developmental Disorders

**Support:** NINDS RO1NS081281

the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

**Title:** Loss of PlxnA2-rasGAP forward signaling impairs the development of the dentate neurogenic niche and leads to schizophrenia-like behaviors

**Authors: *X.-F. ZHAO**[1], R. KOHEN[1], R. PARENT[2], Y. DUAN[1], M. J. KORN[3], D. F. DOLAN[4], J. M. PARENT[3,6], G. G. MURPHY[2,5], R. J. GIGER[1,3]
[1]Cell and Developmental Biol., [2]Mol. and Behavioral Neurosci. Inst., [3]Neurol., [4]Kresge Hearing Res. Inst., [5]Mol. and Integrative Physiol., Univ. of Michigan, Ann Arbor, MI; [6]VA Ann Arbor Healthcare Syst., Ann Arbor, MI

**Abstract:** Overwhelming evidence suggests that Schizophrenia (SCZ) is a neurodevelopmental disorder with a strong genetic underpinning. Genome-wide association studies identified numerous SCZ risk genes, including rare variants of members of the *SEMAPHORIN (SEMA)* family of axon guidance molecules and their receptors the *PLEXINs (PLXNs)*. Human variants of *PLXNA2* lead to reduced *PLXNA2* gene expression in the forebrain and increased SCZ susceptibility. The underlying biology and neural circuitry perturbed by *SEMA/PLXNA2* mutations that can cause SCZ symptoms in patients remain unknown. We show that in mice global *Plxna2* deficiency (*Plxna2*$^{-/-}$) disrupts migration and proliferation of early-born dentate granule cells (GCs) as they travel from the primary neuroepithelium to the dentate gyrus (DG) primordium. Genetic labeling of Nestin$^{+}$ cells in the postnatal *Plxna2*$^{-/-}$ DG revealed a significant

decrease in the stem cell population and reduction in DG overall size. PlxnA2 is expressed by migrating GCs and PlxnA2 forward signaling through its rasGAP domain is required for proper GC migration *in vivo*. Loss of *Sema5A* leads to a similar GC migration defect. *In vitro*, Sema5A/PlxnA2 signaling causes rapid collapse of COS7 cells. Cell collapse depends on a functional PlxnA2-rasGAP domain and the small GTPase Rap1b. Morphological defects in the adult *Plxna2*$^{-/-}$ hippocampus include dispersion of the granule cell layer and aberrant GC-CA3 connectivity, reminiscent of temporal lobe epilepsy. However, *Plxna2*$^{-/-}$ mice are not epileptic, as assessed by EEG recordings with epidural electrodes. Behavioral studies with *Plxna2*$^{-/-}$ mice revealed selective defects in contextual fear conditioning but not in cued fear conditioning. *Plxna2*$^{-/-}$ mice show reduced sociability in the 3-chamber-approach test and a striking reduction of PPI (Pre-Pulse Inhibition) of the acoustic startle response. Selective disruption of the PlxnA2-rasGAP activity recapitulates the PPI phenotype observed in *Plnxa2*$^{-/-}$ mice. Collectively, our studies identify a novel mechanism for GC migration and reveal SCZ-like behaviors caused by disruption of PlxnA2-rasGAP forward signaling. Insights into the neural circuits affected by *PLXNA2* mutations and characterization of the biochemical pathways regulated by PlxnA2-rasGAP signaling may be exploited therapeutically in psychiatric disorders.

**Disclosures: X. Zhao:** None. **R. Kohen:** None. **R. Parent:** None. **Y. Duan:** None. **M.J. Korn:** None. **D.F. Dolan:** None. **J.M. Parent:** None. **G.G. Murphy:** None. **R.J. Giger:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.14/C15

**Topic:** A.07. Developmental Disorders

**Support:** CURE for Epilepsy

NIH NINDS R56NS094889-01A1

NIH NIMH R01MH106623

**Title:** Alteration of cortical-striatal circuits in a new genetic mouse model of infantile spasms and seizures

**Authors: *A. PIRONE**, C. DULLA, M. JACOB
Dept. of Neurosci., Tufts Med. Sch., Boston, MA

**Abstract:** Infantile spasms (IS) constitute a catastrophic childhood epilepsy syndrome characterized by neonatal spasms, lifelong seizures and cognitive deficits. Current frontline medications have mixed efficacy and cause severe side effects. Developing new effective treatments is essential, but requires knowledge of the underlying molecular and functional

changes, and the particular brain regions whose malfunction cause spasms and seizures. To gain insights into the pathophysiology of the disease, we have developed a new genetically modified mouse model of IS with conditional deletion in neurons of adenomatous polyposis coli protein (APC cKO), the major negative regulator of β-catenin/Wnt. The APC, β-catenin, Wnt pathway links to several IS-risk human genes. Further, missense variants in APC, predicted to be damaging, have been identified in individuals with epileptic encephalopathies. These correlations support the importance of elucidating how malfunction of this pathway alters the brain. APC cKO mice exhibit most of the features seen in individuals with IS *(Pirone et al., 2017)*. Neonatal APC cKOs, compared with wild-type littermates, exhibit high amplitude flexion-extension spasms and abnormal EEG recordings. Adult APC cKOs display spontaneous behavioral and electrographic seizures, as well as cognitive impairments. APC cKOs show brain structural changes consisting of corpus callosum agenesis, synaptic spine density on glutamatergic projection neurons, and aberrant organization of processes in the striatum. At the age of peak spasm intensity, postnatal day 9, APC cKOs display increases in excitatory synaptic activity, increased cortical glutamatergic inputs on dorsal striatum medium spiny neurons (MSNs). P9 MSNs also exhibit increases in mEPSC frequency, but no change in amplitude. Cortical-striatal connections function to regulate motor behaviors, and influence the formation of widespread network connections across many brain regions. Interestingly, the neonatal time window of the formation and maturation of cortical-striatal connections correlates with the age of IS-like motor spasms in APC cKOs. Our studies are elucidating whether malfunction of cortical-striatal circuits underlies spasms and progression to chronic seizures. We are also identifying novel molecular targets with potential for new, specifically targeted therapeutic interventions.

**Disclosures:** **A. Pirone:** None. **C. Dulla:** None. **M. jacob:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.15/C16

**Topic:** A.07. Developmental Disorders

**Support:** NRF-2015M3C7A1029113

NRF-2014M3C9A2064619

KRIBB Initiative Research Program

**Title:** The dominant negative effects of genetic mutations identified in developmental delay

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**Abstract:** Many genetic mutations that deteriorate neuronal functions could result developmental delay accompanying intellectual disability. In the hereditary genetic disorders, genetic mutations could be inherited in one of several patterns like autosomal dominant or autosomal recessive or X-linked inheritance. Next generation sequencing have disclosed many variants in one gene that elicit genetic disorders inherited in the different patterns. For example, each mutation in the same gene could result developmental disorders showing autosomal recessive inheritance or autosomal dominant inheritance. It has been suggested that dominant negative effects exerted by mutations elicit autosomal dominant inheritance. Here it might be questioned whether mutations inherited in autosomal recessive disorders could not exert dominant negative effects. We set new strategy to evaluate the degrees of dominant negative effects exerted by each mutation identified from one gene that results developmental delay. In conclusion, dominant negative effect exerted by mutations of autosomal dominant inheritance was stronger than autosomal recessive inheritance. These results suggest that each mutation might exert various degrees of dominant negative effects according to their properties of the mutated amino acids.

**Disclosures:** **J. Lee:** None. **S. Lim:** None. **C. Cheon:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.16/C17

**Topic:** A.07. Developmental Disorders

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Brain Research Foundation

CPRIT

IDDRC U54HD083092

**Title:** Integrative and rapid discovery of wiring molecules

**Authors: B. I. LIU**[1,2], *N. E. ALBRECHT[1,2], D. JIANG[1,2], C. A. BURGER[1,2], F. LI[1,2], J. WANG[3], S.-Y. KIM[6], C.-W. HSU[4], S. KALAGA[4], U. UDENSI[4], C. ASOMUGHA[4], R. BOHAT[5], A. GASPERO[5], K. MAY[1,2], L. LIN[1,2], M. J. JUSTICE[7], S. YAMAMOTO[3,6,5], J. R. SEAVITT[5], A. L. BEAUDET[5], M. E. DICKINSON[3,4,5], M. A. SAMUEL[1,2,3]
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**Abstract:** Synapses are the relay points for information transfer in the nervous system. These remarkably complex connections are required for nervous system function, but surprisingly few genes have been directly linked to synapse integrity. Here, we leverage the resources available through the International Mouse Phenotyping Consortium (IMPC) to Identify Novel Synaptic Integrity Genes by High Throughput screening (INSIGHT). We computationally identify 446 genes of the available 4288 lines that play a role in regulating neural phenotypes. We then characterize 90 unique gene knockouts for novel architectural and synaptic defects using the organizational and functional advantages of murine retina. We evaluated key components of circuit integrity including neuronal and glial anatomy, synaptic lamination and distribution, as well as layer topography and organization. We uncover neural and synaptic regulatory roles for previously uncharacterized genes and document additional biological functions for genes with previously reported neural phenotypes. In addition, several of the synaptic regulatory genes we document play roles in human neural diseases, suggesting that this dataset may facilitate identification of novel disease causing alleles.

**Disclosures: B.I. Liu:** None. **N.E. Albrecht:** None. **D. Jiang:** None. **C.A. Burger:** None. **F. Li:** None. **J. Wang:** None. **S. Kim:** None. **C. Hsu:** None. **S. Kalaga:** None. **R. Bohat:** None. **S. Yamamoto:** None. **J.R. Seavitt:** None. **A.L. Beaudet:** None. **M.E. Dickinson:** None. **M.A. Samuel:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

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**Program#/Poster#:** 463.17/C18

**Topic:** A.07. Developmental Disorders

**Support:** NIH Grant R15NS096562

Whitehall Foundation

**Title:** mTOR-dependent ULK1phosphorylation is rapamycin resistant in neural-derived cells

**Authors:** *A. M. SOKOLOV, ***A. M. SOKOLOV**, D. M. FELICIANO
Biol. Sci., Clemson Univ., Clemson, SC

**Abstract:** The mammalian target of rapamycin (mTOR) is a protein kinase that partitions into two complexes, mTORC1 and mTORC2. mTORC1 stimulates anabolic but inhibits catabolic processes whereas mTORC2 regulates the cytoskeleton and cell survival. Appropriate mTOR activity during brain development is essential for proper formation and optimization of neuronal morphology. One mechanism that may contribute to these events is mTOR inhibitory phosphorylation of the pro-autophagic kinase Ulk1 at serine 757. We found that embryonic day 14.5 to postnatal day 21 forebrain lysates were immunoreactive for pULK1-757 which was detected in maturing neurons. We pharmacologically and genetically perturbed mTOR activity in neuro2a cells to determine the role of mTOR on Ulk1 phosphorylation. These experiments revealed that pUlk1-757 is rapamycin-insensitive but Torin1-sensitive. Genetic manipulations of mTORC1 activity produced proportional changes in pUlk1-757. We propose that the variable success of rapamycin analogues in correcting neurological manifestations in patients with elevated mTOR activity may be related to rapamycin resistance of mTORC1 phosphorylation of Ulk1.

**Disclosures: A.M. Sokolov:** None. **D.M. Feliciano:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

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**Program#/Poster#:** 463.18/C19

**Topic:** A.07. Developmental Disorders

**Support:** NIH Grant R01NS076708

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NIH Grant R01MH112356

**Title:** Making sense of nonsense-mediated decay in neurodevelopmental disorders

**Authors: *J. L. JOHNSON**[1], L. G. STOICA GHITA[2], P. ZHU[1], S. A. BUFFINGTON[1], A. BHATTACHARYA[3], G. STINNET[4], E. ONORATI[1], N. T. EISSA[3], R. PAUTLER[4], B. T. PORSE[6], M. COSTA-MATTIOLI[5]
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**Abstract:** Nonsense-mediated decay (NMD) is an evolutionarily conserved surveillance mechanism that targets mRNAs undergoing premature translation termination as well as normal physiological transcripts for rapid degradation. NMD requires the function of three conserved Up-frameshift (Upf) factors (Upf1, Upf2, Upf3). In humans, mutations in *UPF2* and other NMD components are associated with intellectual disability and autism spectrum disorder (ASD). However, the biological mechanism by which deficient NMD leads to neurodevelopmental disorders remains unknown. Here we report that mice lacking Upf2 in the forebrain (Upf2 fb-KO mice) show learning and memory deficits and abnormal long-term potentiation (LTP) in the hippocampus. Moreover, Upf2 fb-KO mice showed behavioral endophenotypes associated with ASD and neuroanatomical abnormalities including a smaller corpus callosum which has previously been reported in patients with mutations in NMD genes. Given that the Upf proteins are evolutionarily conserved, we also investigated whether Upf2 is required for memory formation in *Drosophila.* Interestingly, long-term memory was impaired in flies with reduced Upf2 levels in the CNS, suggesting an evolutionarily conserved role for NMD in learning and memory. We are currently trying to identify the mRNAs whose expression is altered when NMD is dysfunctional in the brain of Upf2 fb-KO mice and the mechanisms by which impaired NMD causes behavioral and neurophysiological abnormalities.

**Disclosures: J.L. Johnson:** None. **L.G. Stoica Ghita:** None. **P. Zhu:** None. **S.A. Buffington:** None. **A. Bhattacharya:** None. **G. Stinnet:** None. **E. Onorati:** None. **N.T. Eissa:** None. **R. Pautler:** None. **B.T. Porse:** None. **M. Costa-Mattioli:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.19/C20

**Topic:** A.07. Developmental Disorders

**Title:** Expression profiling of autism-related genes and their associated antisense transcripts in medial prefrontal cortex and striatum during mouse brain development

**Authors: B. KOC**, R. SCHMUCKI, D. MALHOTRA, *B. J. HALL
F. Hoffmann-La Roche Ltd., Basel, Switzerland

**Abstract:** Genome-wide sequencing technologies have greatly contributed to our understanding of the genetic basis of autism spectrum disorders (ASD). Interestingly, a substantial number of ASD-related genes also express natural antisense transcripts (NATs). In some cases, these have been shown to play a regulatory role in gene expression and contribute to disease pathogenesis. However, a comprehensive study examining the relationship between ASD-related gene transcripts and their NAT partners is lacking. We used a strand-specific deep RNA sequencing approach (120 million reads/sample) to profile over 100 ASD-related genes and their NATs in a

brain region-specific manner at three discrete time points during mouse brain development. We isolated two ASD-relevant brain regions, medial prefrontal cortex (mPFC) and striatum (Str), from P7, P14, and P56 animals. Our analysis revealed that more than half of the examined ASD-related genes have NAT transcripts including novel ones; suggesting that more ASD-related genes than previously thought could be subject to NAT-mediated regulation. We found that expression levels of NATs were mostly negatively correlated with their related gene partners (~20%, r<-0.90), for example the serine protease, Prss12. However, there was also a small fraction of positively correlated genes identified (~5%, r>0.90), including the ubiquitin protein ligase, Ube3a. A small fraction of the examined NATs also showed region specific enrichment, suggesting potential brain region defining roles. Our findings contribute to the understanding of NAT regulation of ASD-related genes in mice to guide preclinical investigation toward an ultimate goal of developing novel therapeutic approaches in patients by manipulating NAT-mediated gene regulation in ASD.

**Disclosures: B. Koc:** None. **R. Schmucki:** None. **D. Malhotra:** None. **B.J. Hall:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

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**Topic:** A.07. Developmental Disorders

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W.M. Keck Foundation Grant

**Title:** Hyper-excitation during critical developmental periods results in psychiatric behavioral phenotypes

**Authors: *W. E. MEDENDORP**[1], A. PAL[2], R. RIDGELL[2], U. HOCHGESCHWENDER[3]
[1]Neurosci., [2]Central Michigan Univ., Mount Pleasant, MI; [3]Neurosci., Central Michigan Univ., Mt Pleasant, MI

**Abstract:** Early development is marked by spontaneous neuronal activity that occurs without the input of sensory experience. This is best demonstrated in the visual system, but has been shown to be a generalized phenomenon. By manipulating this activity in genetically defined neural populations within the prefrontal cortex, we can interfere with the normal formation of specific neural circuits. Many psychiatric disorders are thought to be neurodevelopmental, stemming

from malformation of neural circuits. These circuits are primarily found within the prefrontal cortex, where our manipulation will take place. Early disruptions to neural activity may result in behavioral changes that correlate with psychiatric phenotypes typical of disorders such as autism, anxiety, or depression. Using optogenetics, we can manipulate neuronal activity using light. Due to the young age of the animals used in this study, a non-invasive light source must be used. Our laboratory has created mice that conditionally express a luciferase protein, sbGLuc, tethered to a channelrhodopsin, VChR1. This luminescent opsin, or luminopsin (LMO3), produces light, and thus a neuronal response, in the presence of the substrate coelenterazine (CTZ), which can be delivered intraperitoneally (ip). Lox-Stop-Lox LMO3 mice were crossed with Cre driver lines (Emx-1, Dat), thus limiting expression of LMO3 to neuronal populations of interest. By delivering CTZ ip during post-natal days 4-14, alterations in the firing activity of specific neuronal populations can be induced in developing mouse pups. During adulthood, mice are then tested for depressive, anxiety, antisocial, and general locomotive behaviors. The results of this research will provide insight into the effect of altered developmental activity and its relationship to psychiatric disease.

**Disclosures: W.E. Medendorp:** None. **A. Pal:** None. **R. Ridgell:** None. **U. Hochgeschwender:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.21/C22

**Topic:** A.07. Developmental Disorders

**Title:** GNAS, a new epigenetic player in cortical neurodevelopment and sleep architecture

**Authors: *C. GARCIA-GARCIA**[1], E. BALZANI[1], C. CHIABRERA[1], E. ALBANESI[1], M. MAZZI[2], F. NICASSIO[2], L. CANCEDDA[1], V. TUCCI[1]
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**Abstract:** Recent evidence has pointed out that imprinted genes, which exert fundamental roles in embryonic development, are also important in the regulation of sleep and cognitive processes in adulthood. Moreover, sleep abnormalities and cognitive impairment are hallmarks of several neurodevelopmental disorders, suggesting that neurodevelopment is pivotal for the formation of sleep and cognition. However, the link between developmental mechanisms and sleep remains largely unknown. Recently, our group has demonstrated that loss of imprinting in the GNAS locus dramatically affects sleep physiology and cognitive functions in mice. GNAS main product, Gαs, codifies for the G protein α-subunit, one of the main players for intracellular cAMP generation in the central nervous system. In order to further understand the role of Gαs in neural development and sleep formation, we downregulated the expression of Gαs (by *in utero*

electroporation, IUE) in progenitors of the pyramidal neurons committed to upper layers of the prefrontal cortex in mice. We found that Gαs is involved in pyramidal neuron migration and morphological maturation. Specifically, Gαs defective neurons are characterized by more and longer branches; and notably, 20% of them are misplaced in the layer I of the prefrontal cortex. A total RNA sequencing of these IUE neurons supported our previous data indicating that Gαs is implicated in several processes controlling neurodevelopment and neural migration. New potential roles for this gene, not yet described in literature, are being confirmed. Moreover, we report that downregulation of Gαs staring from embryonal stages has also a modulatory effect on sleep in adult mice with an increase in NREM sleep and an anticipatory tendency to fall sleep after 6 hours of sleep deprivation. This proves that the imprinted gene Gαs, is responsible of the homeostatic control of sleep in prefrontal cortex circuits. Overall, this work provides new insights into the link between genomic imprinting, neurodevelopment and sleep.

**Disclosures: C. Garcia-Garcia:** None. **E. Balzani:** None. **C. Chiabrera:** None. **E. Albanesi:** None. **M. Mazzi:** None. **F. Nicassio:** None. **L. Cancedda:** None. **V. Tucci:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

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**Program#/Poster#:** 463.22/C23

**Topic:** A.07. Developmental Disorders

**Support:** NIH R01-NS056314

**Title:** Inducible knockout of Lis1 in adult mice causes death following a progressive decline in autonomic functions

**Authors: *T. J. HINES**, S. SAHU, J. L. TWISS, D. S. SMITH
Biol. Sci., Univ. of South Carolina, Columbia, SC

**Abstract:** *Lis1* haploinsufficiency causes developmental brain abnormalities in humans and mice. Total loss of Lis1 is lethal early in embryogenesis. The cellular defects of Lis1 deficiency during development are often linked to its interactions with cytoplasmic dynein, a molecular motor that regulates spindle dynamics, cell migration, and intracellular transport. Lis1 expression remains high in adult rodent brains and we have found that Lis1 modulates dynein-dependent axon transport in cultured adult rat sensory neurons. We now report that Lis1 has a vital role in adult animals, as tamoxifen-inducible, Cre-ER mediated recombination led to rapid decline and death of all animals that carried the Cre-ER allele and the floxed Lis1 allele. Although Cre-ER expression was under the control of an actin promoter, tamoxifen-induced Cre activation was not uniform, occurring with different time delays in different cell types in multiple tissues including brain, heart, liver, kidney, lung, and muscle. In the brain, the most pronounced regions of Cre

activity were found in the midbrain, hindbrain and cerebellum. Cre activity was also prominent in peripheral neurons, and in cardiac and skeletal muscle. Mice were apparently healthy and fertile when activation of Cre was limited to cardiac muscle, so the drastic phenotype observed is likely due to a critical role of Lis1 in adult nervous tissues. Axon transport defects and an increase in the number of axonal varicosities are observed in cultured sensory neurons from KO mice. Additionally, there is an increase in the number of chromatolytic neurons in the brainstem of KO mice. These findings support a role for Lis1 in regulating axon transport in adult animals. The exact mechanisms underlying the neuronal pathology observed are being investigated further.

**Disclosures:** **T.J. Hines:** None. **S. Sahu:** None. **J.L. Twiss:** None. **D.S. Smith:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

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**Program#/Poster#:** 463.23/C24

**Topic:** A.07. Developmental Disorders

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Klingenstein-Simons Neuroscience Fellowship

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NARSAD Young Investigator Award from the Brian and Behavior Research Foundation

**Title:** Mosaic mutations contribute to autism spectrum disorder risk

**Authors: *R. BARNARD**[1], D. R. KRUPP[1], S. A. EVANS[1], Y. DUFFOURD[2], R. M. MULQUEEN[1], R. BERNIER[3], J.-B. RIVIÈRE[4], E. FOMBONNE[1], B. J. O'ROAK[1]
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**Abstract:** Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a strong yet complex genetic architecture. Recently, postzygotic mosaic mutations (PMMs), which arise after embryo fertilization and result in a mosaic mixture of mutated and non-mutated cells, have been implicated in overgrowth and neurodevelopmental disorders. Compared to germline variation, the mosaic nature of these mutations makes them inherently difficult to detect and validate. In previous ASD exome studies, we surprisingly found 5% of *de novo* mutations validated as

mosaic. Here, we sought to address the role exonic PMMs may play in ASD risk. We first re-evaluated previously published exonic *de novo* single nucleotide variant (SNV) mutations from a large cohort of ASD simplex families, the Simons Simplex Collection (SSC). We found 11% of these mutations showed characteristics consistent with putative PMMs. We then developed a robust and more sensitive custom PMM calling approach and high-throughput validation method to systematically evaluate PMMs within the SSC exome data. This approach leverages complementary callers, logistic regression modeling, and additional empirically determined heuristics. Applying this approach, we identified 470 PMMs in SSC children, 398 of which were not previously published as *de novo* mutations. PMMs comprised 22% of all SNV *de novo* mutations present in SSC children. Surprisingly, we found that probands had a significant burden of synonymous PMMs. Using multiple independent splicing prediction algorithms, we found probands are enriched for synonymous PMMs predicted to impact splicing. We did not observe a similar increased burden of missense PMMs. However, when we looked specifically at probands who do not already have a nonsynonymous germline mutation, we do see a stronger burden signal, particularly for PMMs impacting genes intolerant to mutation. These PMMs overlap high confidence ASD and neurodevelopmental disorder risk genes, suggesting common ASD risk targets for germline and mosaic mutations. We also identified PMMs in novel candidate risk genes associated with chromatin remodeling and neurodevelopment. We also evaluated PMMs in parents and find that 7-11% of parental mosaics are transmitted to children This equated to 6.8% of mutations appearing newly germline in the children occurring postzygotically in parents and underscores important implications for recurrence risk. Overall, we estimate that SNV PMMs contribute risk to 4-8% of simplex ASD cases. These findings argue for a role for SNV PMMs in ASD risk, similar in magnitude to other classes of *de novo* mutations, which warrants continued study in ASD and related disorders.

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**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 463.24/C25

**Topic:** A.07. Developmental Disorders

**Support:** PHC grant 32508PH

**Title:** Descending control dysfunctions related to pain hypersensitivity in a pharmacological mouse model of attention deficit hyperactivity disorder (ADHD)

**Authors: O. BOUCHATTA**[1], S. BA M'HAMED[2], R. B. BENAZZOUZ[1], N. KEREKES[3], P. FOSSAT[1], M. BENNIS[2], *M. LANDRY[1]
[1]Univ. Bordeaux, Bordeaux, France; [2]Univ. Cadi Ayyad, Marrakech, Morocco; [3]Univ. West, Trollhättan, Sweden

**Abstract: Aims:** Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by impaired attention and hyperactivity-impulsivity. Recent evidence pointed to pain hypersensitivity in adults with ADHD. The most widely used neurodevelopmental model of ADHD is obtained by neonatal brain lesion with 6-hydroxydopamine (6-OHDA) in rodents. Our objectives are **1)** to assess the symptoms of the 6-OHDA-mediated dopamine depletion model in mouse. **2)** To analyse comorbid pain behavior in this model. **3)** To highlight circuits and mechanisms underlying pain alterations in ADHD mouse model.
**Methods: 1)** We generated a mouse model at P5 by neonatal disruption of central dopaminergic pathways with 6-OHDA. To assess ADHD-like symptoms, spontaneous activity was evaluated after weaning (P24). At P40 (adulthood), anxiety, working memory, social interactions, inattention and impulsivity were assessed. **2)** We analyzed nociceptive responses to thermal and mechanical stimuli by using hot plate, acetone-evoked cooling and von-Frey filaments. **3)** Spinal neuron activity was further examined *in vivo* by unit recording after mechanical stimulus. Finally, we explored if the anterior cingulate cortex (ACC) is involved in the dysfunction of descending controls in ADHD-like mice. Hence, we recorded ACC activity, and the effects of ACC activation on mechanical stimuli-evoked responses in spinal cord wide-dynamic-range (WDR) neurons.
**Results: 1)** At P24, ADHD-like mice exhibited hyperactivity. At P40, ADHD-like mice showed anxiety, antisocial behavior, increased aggressiveness, and mildly impaired short-term memory. We also demonstrated attention deficit and increased impulsivity in ADHD-like mice. **2)** Mice with neonatal dopamine depletion exhibited a marked increase in both thermal and mechanical sensitivity. Dopamine depletion also increased pain sensitivity in persistent pain conditions. **3)** Electrophysiological recordings showed increased neuronal activity in response to both innocuous and noxious stimuli in the ADHD-like group. Moreover, our data indicated that ACC neurons are hyper-activated in ADHD-like mice. Finally, we found that the electrical stimulation of controlateral ACC increased the responses of WDR neurons to innocuous and noxious stimuli. Our results demonstrated the validity of the neonatal 6-OHDA model to mimic ADHD syndrome. Taken together, our data demonstrated that ADHD conditions induced pain hypersensitivity that is likely mediated by alterations of descending controls and hyperactivation of WDR spinal cord neurons. We also suggest that the deregulation of ACC may be at the origin of descending control dysfunction.

**Disclosures: O. Bouchatta:** None. **S. Ba M'Hamed:** None. **R.B. Benazzouz:** None. **N. Kerekes:** None. **P. Fossat:** None. **M. Bennis:** None. **M. Landry:** None.

**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

**Location:** Halls A-C

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**Topic:** A.07. Developmental Disorders

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EPSRC DTP (EP/L505079/1)

**Title:** Further evidence supporting a role of the dyslexia susceptibility gene KIAA0319 in neuronal migration revealed by a novel technique that investigates cellular forces

**Authors: *R. DIAZ**[1], N. M. KRONENBERG[2], P. LIEHM[2], A. MARTINELLI[1], M. C. GATHER[2], S. PARACCHINI[1]
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**Abstract:** Dyslexia is a disorder with a strong heritable component. Several dyslexia candidate genes affect brain development through their role in cilia. Cilia are small organelles that protrude from the surface of the cell and have a function in crucial developmental events such as cell differentiation and migration. *KIAA0319* is a dyslexia susceptibility gene of unknown function highly expressed in brain during embryonic development and also expressed in ciliated tissues. Experiments in rats suggest that KIAA0319 plays an important role in neuronal migration, a process essential for the formation of brain cortex. KIAA0319 is a transmembrane protein that contains five extracellular PKD domains. This structure is consistent with its proposed role in cell migration, as PKD domains are thought to be involved in the interaction of the cell with specific external molecules.
To assess the effect of KIAA0319 in cilia formation and function, and to investigate its effects in migration and cell adhesion, we have created KIAA0319 knockouts in RPE1 human cell line using CRISPR-Cas9. RPE1 are ciliated cells derived from human retina pigmented epithelium commonly used to study ciliogenesis and cilia function. We have used these knockout cell lines to characterize the mechanical forces cells exert during migration using Elastic Resonator

Interference Stress Microscopy (ERISM). ERISM is a recently developed functional imaging modality for the mapping of cellular forces, which allows for continuous monitoring of mechanical cell-substrate interactions over long periods of time and with high displacement resolution (Kronenberg et al., 2017, accepted). Contrary to other techniques to measure cell forces, ERISM requires no zero-force reference which enables long-term studies and allows further investigation of cells, e.g. by immunostaining.
Our results show that the knockout of KIAA0319 has an effect in cell motility, migration and attachment, three processes that depend on cytoskeleton dynamics. KIAA0319 knockouts apply stronger forces to the substrate and have slower movements compared to the wild type. In addition, we have found that the force patterns exerted during migration vary significantly between wild type and knockout cells, and that the cells show different behavior when their cytoskeleton function is disturbed by inhibition of actin polymerization. These results point to a possible role for KIAA0319 in triggering cytoskeleton responses and, given its transmembrane location, suggest a role of KIAA0319 as signal transducer of extracellular cues.
The result of this study is the first evidence of the role of KIAA0319 in neuronal migration on a cellular level.

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**Poster**

**463. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms I**

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**Topic:** A.07. Developmental Disorders

**Support:** Young investigator project 2008” by Ministry of Italian Health to L.A.R.

**Title:** A disintegrated interface in the prefrontal cortex of a rat animal model for the attention deficit hyperactivity disorder (ADHD)

**Authors: E. CARBONI**[1], D. VALLONE[2], L. A. RUOCCO[3], C. TRENO[3], U. A. GIRONI CARNEVALE[3], G. BOATTO[4], A. TINO[5], *A. G. SADILE[3]
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**Abstract:** The Naples High-Excitability (NHE) rat is a well-known animal model system for ADHD that show hyperactivity and impaired non-selective and selective attention associated with increased activity in the mesocortical dopamine (DA) branch. A Subtractive library study

on Prefrontal Cortex (PFC) has shown that the NMDAR1 glutamate receptor gene was hyper-expressed in NHE compared to Random Bred control rats (NRB). The aim of this study was on three levels: i) to investigate the proteic level of NMDAR1 glutamate receptor subunit in the PFC, by western-blot analysis; ii) to clarify the functional relevance of the higher NMDAR1 expression, by behavioral analysis after acute treatments with different concentrations of the non-competitive antagonist MK801; iii) to study the plasticity of the NMDAR1 system after subchronic MK801 treatments by behavioural analysis in NHE and NRB rats. To this aim young-adult male rats of NHE and NRB lines were used. In exp. 1 western-blot analysis was carried out on left and right hemisphere separately. In exp. 2 acute MK801 (0.0, 0.0001, 0.001, and 0.01 mg/kg) was given intraperitoneally (i.p.). Finally, in exp. 3, subchronic MK801 (0.01 mg/kg) was given i.p. daily over 14 days. Then, NHE and NRB rats were exposed to a spatial novelty (Làt-maze) where horizontal (HA) and vertical (VA) activity were monitored. The results confirmed the higher level of NMDAR1 subunit expression in the left PFC of NHE rats, as previously observed with the Subtractive library assay. In particular, the higher level of NMDAR1 in NHE accounted for 30% of NRB rats. Acute treatments with MK801 increased HA in both NHE and NRB rats at the dose of 0.01mg/kg only. In contrast, MK801 exerted an inverted-U action upon VA frequency and the highest dose decreased its duration in NRB rats only. After subchronic treatment with MK801, the level of the NMDAR1 subunit increased in the PFC of NRB rats by 78%. Moreover, the latter finding was not associated with a higher activity level. In conclusion, the higher level of the NMDAR1 subunit in the PFC of NHE rats reveals a disintegrated interface due, supposedly, to lack of glutamate inputs from anterior thalamus and up-regulation of postsynaptic sites. Data demonstrate that this disintegrated prefrontal interface does not produce a hyperactivity but rather is expressed through an altered nonselective attention. In turn it may reflect an unbalanced glutamate control of prefrontal output leading eventually to distorted prefronto-striatal neurotransmission.

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**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.01/C28

**Topic:** A.09. Adolescent Development

**Support:** U01 AA019972

P50 AA017823

**Title:** Extrasynaptic $GABA_A$ receptors in age-related differences to ethanol responsively during social interaction

**Authors: J. M. CARTER**, C. A. DANNENHOFFER, *D. F. WERNER, L. P. SPEAR
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**Abstract:** Adolescents differ from adults in terms of responsiveness to a number of ethanol effects that may serve to promote higher intake during adolescence, but the neural underpinnings of these age differences have yet to be detailed. Given that prior studies suggest that extrasynaptic $GABA_A$ receptor tonic inhibition is attenuated in adolescents, but more sensitive to ethanol compared to adults (Fleming et al., 2007), the current study further characterized age-related differences in the $GABA_A$ receptor delta subunit commonly associated with extrasynaptic receptors as well as their regulation following ethanol exposure in late developing regions. Social interactions as well as locomotor activity/sedation were used to dose-dependently assess potential age differences in the effects of pharmacological stimulation of $GABA_A$ receptors containing this subunit. For biochemical analyses, tissue was isolated from adolescent (P35) and adult subjects (P75) and processed for synaptosomal analysis. For behavioral studies, subjects were injected (i.p.) with 0.0, 1.0, 2.0 or 4.0 mg/kg of the selective $GABA_A$ receptor agonist THIP that demonstrates a preference for delta subunit-containing $GABA_A$ receptors. Animals were then placed alone in a novel social interaction chamber for 30 minutes during which time locomotor activity was assessed prior to introduction of an unfamiliar age- and sex-matched partner for a 10 minute social interaction test. Sessions were recorded for later assessment of social behaviors and social preference/avoidance. Intoxication ratings were also conducted using the Chandler/Crews rating scale. Results indicate that $GABA_A$ receptor delta subunit basal expression was noticeably reduced in the hippocampus and prefrontal cortex of adolescents compared to adults. Preliminary data further suggest that delta subunits are down-regulated 1 hour following a moderate dose of ethanol in adolescents, but not in adults. Behaviorally, the delta-containing receptor selective agonist THIP increased initial locomotor activity during habituation, followed by dose-dependent sedation, corresponding increases in social inhibition, and significant intoxication ratings – effects that were evident in adolescents but not in adults. Taken together, these results suggest that activity at delta-containing extrasynaptic $GABA_A$ receptors parallels the locomotor stimulant and sedative/intoxicating behavioral responses of ethanol, and that their down-regulation may be contributing factor in age-dependent differences in ethanol-induced social inhibition, likely a result of sedation.

**Disclosures: J.M. Carter:** None. **C.A. Dannenhoffer:** None. **D.F. Werner:** None. **L.P. Spear:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.02/C29

**Topic:** A.09. Adolescent Development

**Support:** National Research Foundation of Korea (NRF)

**Title:** In adolescence, elevation of GABA activity in the dentate granule cell induced by neonatal maternal separation is related with reduction of dentate gyrus-CA3 synaptic plasticity, anxiety- and aggressive-like behavior

**Authors: *S. SHIN**, S. MIN
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**Abstract:** Neonatal maternal separation (MS) is one of the animal models for emotional disorder such as anxiety and depression. Thus far, MS study has been done by many researchers on many different kinds of species from rats to apes and produced a lot of behavioral results. However, the effects of MS on the synaptic plasticity of the hippocampus remain imperfect understanding. This study investigated the effects on the behavioral changes and mechanisms of the synapse plasticity in the hippocampus in MS mice. Following a periodic neonatal MS (4-hour a day, during 19 days), adolescent mice were employed for behavioral experiments for depression, learning, memory, anxious and aggressive behavior using the forced swimming test (FST), Y-maze, Morris water maze (MWM), elevated plus maze (EPM), three consecutive days of the open field test, the social interaction test, the tube-dominance test and the resident-intruder test. The results showed that there was no difference in FST, Y-maze, and MWM performance. However, MS mice showed more anxiety-like behavior in the EPM test and aggressive-like behavior in the tube-dominance and resident-intruder tests. In addition, the magnitude of long-term potentiation (LTP) and release probability in the dentate gyrus (DG)-CA3 synapses were significantly reduced in the MS group but not in the CA3-CA1 synapse. Thereafter, the excitatory postsynaptic currents (EPSCs) and inhibitory postsynaptic currents (IPSC) were measured in the hippocampal dentate granule cells by using patch clamp recording. MS mice showed elevated gamma-aminobutyric acid$_A$ ($GABA_A$) receptor-mediated IPSCs in the ventral hippocampal dentate granule cell. These results indicate that early life stress based on MS may induce anxiety- and aggressive-like behavior during adolescence, and these behavioral alterations are associated with reduced synaptic plasticity and release probability at the DG-CA3 synapses. In addition, these changes can be associated with the elevation of the $GABA_A$ receptor-mediated IPSCs in the ventral hippocampal dentate gyrus, although the precise mechanism between the alterations of behavior and the synaptic plasticity remains to be elucidated.
Acknowledgments — This study was supported by the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology, grant number NRF-2017001077.

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grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Research Foundation of Korea.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

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**Topic:** A.09. Adolescent Development

**Support:** NIH Grant AA024890-01A1

NIH Grant AA01782306

**Title:** Adolescent stress induces long-lasting increases in social anxiety: A role for basolateral amygdala kappa opioid receptors

**Authors: *M. R. DIAZ**[1], J. HERMAN[3], T. DEAK[4], E. I. VARLINSKAYA[2]
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**Abstract:** Adolescence is a developmental period marked by robust neural alterations and heightened vulnerability to stress, a factor that is highly associated with increased risk for emotional processing deficits, such as anxiety. Stress-induced upregulation of the dynorphin/kappa opioid receptor (DYN/KOR) system is thought to underlie the negative affect associated with stress. The basolateral amygdala (BLA) is a key structure involved in anxiety, and neuromodulatory systems, such as the DYN/KOR system, can 1) regulate BLA neural activity in an age-dependent manner in stress-naïve animals and 2) underlie stress-induced anxiety in adults. However, the role of the DYN/KOR system in modulating stress-induced anxiety in adolescents or the long-lasting effects of adolescent stress are unknown. To test this, we have assessed the impact of an acute, 2-day forced swim stress (FSS - 10 min each day) on adolescent (~postnatal day (P) 35) and adult Sprague-Dawley rats (~P70) using behavioral, molecular and electrophysiological techniques. Adolescent males, but not adult males or females of either age, demonstrate social anxiety-like behavioral alterations indexed via significantly reduced social interaction/preference when tested 24 hr following FSS. While there are no FSS-induced changes in expression of genes related to the DYN/KOR system in the BLA, these behavioral alterations are associated with a robust switch in BLA KOR function consistent with an anxiogenic phenotype. Furthermore, adolescent-stressed males display persistent reduced social behavior in adulthood, which is significantly exacerbated by a 2$^{nd}$ stressor in adulthood. This is the first study to demonstrate a KOR-dependent mechanism that underlies adolescent- and sex-specific social anxiety induced by stress. Importantly, these findings provide evidence

for potential KOR-dependent mechanisms that may contribute to pathophysiological interactions with subsequent stress challenges.

**Disclosures:** **M.R. Diaz:** None. **J. Herman:** None. **T. Deak:** None. **E.I. Varlinskaya:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

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**Topic:** A.09. Adolescent Development

**Support:** PIRE-NSF-OISE-1545803

**Title:** Nandrolone during adolescence increase sensitization to cocaine in juvenile, but not in adult male rats

**Authors: J. A. FREIRE, Mr.**, C. J. RIVERO, Mr., *A. C. SEGARRA
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**Abstract:** The use of anabolic androgenic steroids (AAS) by adolescents is rising. Adolescents seek AAS because of their anabolic properties, unaware of the effects these might have on the developing reproductive and nervous system. Previous studies show that AAS cross-sensitize with other drugs of abuse such as cocaine. We investigated the effect of AAS exposure during adolescence on cocaine sensitization during adolescence (day 40) and adulthood (day 60) in male rats. For 10 consecutive days, starting on day 28, adolescent male rats received daily injections of nandrolone decanoate (20mg/kg/sc) or of vehicle. When they reached 40 or 64 days of age, they were tested for locomotor sensitization to cocaine. From days 1-5 and at days 13 and 23 rats received an injection of cocaine (15 mg/kg/ip). Their locomotor response to cocaine was measured at days 1, 5, 13 and 23. Nandrolone exacerbates the acute response to cocaine in juveniles as well as in adult rats.
Rats tested as juveniles sensitized to cocaine only when re-exposed to cocaine after a 7 day withdrawal period. However, those treated with nandrolone showed sensitization after 5 days of repeated cocaine administration. In comparison, rats tested as adults sensitized to cocaine after 5 days of repeated cocaine administration, whereas those treated with nandrolone did not show a progressive increase in locomotor activity after repeated cocaine administration. These data indicate that exposure to AAS during adolescence exert long lasting effects on the locomotor activating effects of cocaine.

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**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

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**Program#/Poster#:** 464.05/C32

**Topic:** A.09. Adolescent Development

**Title:** Akt signaling is involved in neonatal stress-induced autistic-like behaviors

**Authors: *X. ZHANG**, Z. ZHOU
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**Abstract:** The serine/threonine kinase Akt, also known as protein kinase B, plays an essential role in diverse signaling transduction pathways, such as cell survival, proliferation, apoptosis, cell migration, glucose metabolism and cell-cycle progression. A critical period of brain development refers to a specific time window during early postnatal life, when the brain is extremely flexible to acquire certain information or environment stimuli. It is known that brain circuits can be shaped by experience during critical period, which modulates adult emotion, cognition and behaviors. Although accumulating studies have indicated that aberrant Akt signaling underlies pathogenesis of complex human disorders including diabetes, cancer and neurological diseases, little is known about the function of Akt signaling in brain development during the critical period. We employed maternal separation, a commonly used early life stress model, to investigate the functions of Akt signaling cascade in neonatal brain development. With a combination of behavioral, electrophysiological and biochemical assays, our results suggest an important role of Akt signaling in synaptic modulation during the critical period, and that neonatal stress may cause autistic-like behaviors in adult mice through the Akt signaling pathway.

**Disclosures: X. Zhang:** None. **Z. Zhou:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.06/C33

**Topic:** A.09. Adolescent Development

**Title:** Interacting effects of caffeine and nicotine on anxiety-like behavior but not on locomotion and conditioned place preference

**Authors: *A. D. TAVARES**[1], P. H. L. ROCHA[1], F. NUNES[1], A. C. MANHAES[1], C. C. FILGUEIRAS[1], A. R. CARVALHO[2], Y. A. VILLAÇA[1]
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**Abstract:** Caffeine and nicotine are on top of the list of psychoactive substances consumed in the world. Epidemiological data demonstrate that co-consumption is frequent and experimental studies provide evidence of interactions between these drugs. Caffeine is consumed throughout life, while smoking usually starts during adolescence.
Accordingly, the objective of this study was to evaluate, during adolescence of Swiss mice, the effects of chronic exposure to caffeine on the susceptibility to nicotine. Caffeine exposure extended from the first day of mating until the last day of the behavioral tests. The animals were split into 3 experimental groups: CAF0.3 - free access to caffeine 0.3g/L as the only source of liquid (n=13 litters); CAF0.1 - free access to caffeine 0.1g/L as the only source of liquid (n=8 litters); control group (CG) - free access to drinking water (n=10 litters). On PN30 (PN = post natal day), animals from each litter were submitted to the conditioned place preference (CPP) or open field (OF) test. In the CPP, the time spent in the chamber paired with nicotine (0.5mg/Kg, i.p.) before and after conditioning was analyzed. In the OF, nicotine (0.5mg/Kg, i.p.) or saline was administered immediately before the test. We evaluated total ambulation (locomotor activity) and the time spent in the center of the arena (as a measure of anxiety-like behavior). Mice developed preference for the nicotine-paired compartment in the CPP and caffeine failed to interfere with the effect of nicotine ($F_{1.39} = 11.4$; $p \leq 0.01$). In the OF, acute nicotine increased locomotion, and chronic caffeine exposure failed to affect this nicotine-evoked response ($F_{1.112} = 8.5$; $p \leq 0.01$). Interestingly, caffeine was anxiogenic at the higher dose ($F_{2.51} = 3.9$; $p \leq 0.05$; CAF0.3 ≤ CG; $p=0.05$; CAF0.3 ≤ CAF0.1; $p=0.05$), and this effect was reversed by nicotine. Altogether, these data suggest that chronic caffeine exposure does not alter reward properties of nicotine during early adolescence. Nevertheless, functional interactions between these drugs were identified in the anxiety-like behavior, requiring further studies to better understand the mechanisms that underlie these interactions.

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**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

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**Program#/Poster#:** 464.07/C34

**Topic:** A.09. Adolescent Development

**Title:** Puberty-dependent and puberty-independent regulation of exploration, novelty seeking, and social motivation across adolescent development

**Authors: R. F. KYNE**[1], Q. E. CARROLL[2], L. M. BROWN[2], K. C. SCHATZ[2], A. C. HO[2], L. LIN[2], *M. J. PAUL[2]
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**Abstract:** Alongside the activation of pubertal hormones, adolescents exhibit marked increases in risk-taking, novelty seeking, and social interaction. Whether these adolescent changes are driven by, or merely coincide with, elevated pubertal hormones has been difficult to discern. Seasonal breeders that delay pubertal development during the non-breeding season could provide unique opportunities to investigate the role of pubertal hormones in adolescent development in structurally and genetically intact animals. Siberian hamsters (*Phodopus sungorus*) born in long, summer-like day lengths (LDs) undergo rapid pubertal development, whereas those born in short, winter-like day lengths (SDs) delay puberty by 5 months to synchronize their breeding with the following spring. If pubertal hormones drive the behavioural changes seen across adolescence, these changes should be delayed in SD-reared hamsters. Here, we asked 1) whether LD-reared hamsters increase exploration, novelty seeking, and social motivation during adolescence, and if so, 2) whether their developmental profile is delayed in SD-reared hamsters. Male and female LD- and SD-reared hamsters were tested in the light/dark box, novel object, and social approach tests as juveniles (postnatal day [P]20), early-adolescents (P30), late adolescents (P45-50), young adults (P70-90), or adults (P195-235) to assess developmental changes in the above-mentioned behaviours. For both male and female LD-reared hamsters, exploration (time spent in the light portion of the arena), novelty seeking (time spent investigating a novel object), and social motivation (time spent investigating a novel animal) increased during adolescence and subsequently declined in young adults (exploration and novelty seeking) or adults (social motivation). SD-rearing did not alter the timing of developmental increases in these behaviours. The developmental decline in exploration and novelty seeking, however, was delayed to coincide with puberty, and this was particularly striking in females. Pubertal influences on the decline in social motivation could not be assessed because of the late decline in LD-reared hamsters. These data suggest that the developmental rise in exploratory drive, novelty seeking, and social motivation during adolescence is regulated by puberty-independent mechanisms, whereas the decline in exploration and novelty seeking is brought about by puberty-dependent mechanisms. Ongoing experiments are using the Siberian hamster model to investigate the neural and endocrine substrates that mediate puberty-dependent and puberty-independent influences on adolescent-typical behaviours.

**Disclosures:** **R.F. Kyne:** None. **Q.E. Carroll:** None. **L.M. Brown:** None. **K.C. Schatz:** None. **A.C. Ho:** None. **L. Lin:** None. **M.J. Paul:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

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**Title:** Ketamine treatment during late adolescent impairs with structure-specificity the inhibitory synaptic transmission and working memory during adulthood

**Authors: *M. PÉREZ LIZAMA, SR**[1], C. MORALES[1], O. SANTANDER[1], I. GOMEZ[2], P. R. MOYA[2], M. FUENZALIDA[2]
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**Abstract:** Repeated insults during adolescence leads to dysregulation GABAergic system, a disruption that confers several behavioral and pathophysiological features in rats that resemble human schizophrenia (SZ). The N-Methyl-D-Aspartate receptor (NMDAR) hypofunction model suggest that SZ is associated with loss of NMDAR on corticolimbic parvalbumin positive (PV+)-expressing GABAergic interneurons, leading to disinhibition of pyramidal cells and cortical desynchronization. However, the presumed changes on GABAergic system in both medial prefrontal cortex (mPFC) and hippocampus (HPC) have not been tested yet. Here, we examined whether administration of NMDAR antagonist ketamine (Ket) during late adolescent period results in long-lasting deficits in behavior, neurochemical levels, and GABAergic synaptic transmission in the adult mPFC and HPC. Prolonged exposure of Ket induces long-lasting changes on behavior during adulthood, such as anxiety-like behavior, social withdrawal, and impairment of WM-PFC dependent. Moreover, Ket-treatment reduced PV+ and GAD67 levels on mPFC, without alterations on HPC. However, Ket-treatment did not cause changes in amphetamine-induced hyperlocomotion, which is related to GABAergic normal system on HPC. At neuronal levels, Ket-treatment reduces the frequency of both spontaneous inhibitory postsynaptic current (sIPSC) and miniature (mIPSC) respectively. Ket-treatment modifies the short-term synaptic plasticity: reducing paired pulse depression (PPD) and decrease the synaptic depression during a 10 Hz stimulus train. Together, our results provide a strong experimental support for hypothesis that cortical functions are more susceptibility to derangement by NMDAR hypofunction than HPC during late adolescence, showed apparent structure specificity. Thus,

mPFC could be a primary site of schizophrenia pathogenesis during late adolescent period by neurochemical and GABAergic changes.

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**Poster**

**464. Animal Models of Brain: Environment Interactions**

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**Topic:** A.09. Adolescent Development

**Support:** R01-MH086507

R01-MH105488

**Title:** Developmental regulation of prefrontal plasticity by endocannabinoid-CB1R signaling *In vivo*

**Authors: *H. M. MOLLA**, D. R. THOMASES, K. Y. TSENG
Dept. of Cell. and Mol. Pharmacol., The Chicago Med. Sch. At RFUMS, North Chicago, IL

**Abstract:** Prefrontal cortex (PFC) maturation during adolescence is characterized by structural and functional changes, which involve the remodeling of GABAergic and glutamatergic transmission, as well as changes in endocannabinoid mediated signaling. Despite the modifications that occur within each of these systems, the manner in which the endocannabinoid system interacts with glutamate and GABA transmission in the PFC during the adolescent transition remains unknown. To address this, we conducted local field potential recordings *in vivo* and examined how manipulations of the endocannabinoid-CB1R system affects PFC responses to basolateral amygdala (BLA) and ventral hippocampal (vHipp) stimulation. Pharmacological activation and inactivation of CB1Rs revealed that the recruitment of endocannabinoid-CB1R signaling does not become functionally online until adulthood. Once present, CB1R signaling exerts inhibitory control over both LTP and LTD from afferents originating from the BLA and vHipp. Importantly, this modulation primarily involves the endocannabinoids 2-AG, and anandamide, although the effects of the former are more dominant. Furthermore, our results indicate that CB1R signaling exerts a more powerful inhibitory control of the BLA to PFC transmission. Together, these results show that the endocannabinoid-CB1R signaling in the PFC is developmentally regulated and emerges to control the gain of afferent drive.

**Disclosures:** **H.M. Molla:** None. **D.R. Thomases:** None. **K.Y. Tseng:** None.

**Poster**

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**Topic:** A.09. Adolescent Development

**Support:** NIAAA Grant P50 AA017823

**Title:** Prenatal ethanol exposure reduces sensitivity to the aversive effects of ethanol in adolescence and increases later preference for a 5% ethanol solution in males but not females

**Authors: *J. K. GORE-LANGTON**, L. P. SPEAR
Binghamton Univ., Binghamton, NY

**Abstract:** Insensitivity to the aversive effects of ethanol (EtOH) has been suggested to increase the risk of developing problem drinking behaviors (Schramm-Sapyta et al., 2010). Such aversive effects have been reported to be attenuated in infant rats following EtOH exposure late in gestation (Pautassi et al, 2012). To further examine effects of gestational EtOH exposure on later EtOH aversion and intake, we first investigated the impact of intragastric administration of a moderate dose (2 g/kg) of 20% EtOH from gestational days 17-20 on the aversive effects of EtOH indexed via conditioned taste aversion (CTA) in early adolescence (postnatal days [P] 28-34). Beginning on P 28 (+/- 1 day), male and female Sprague-Dawley rats were given 30 min access to a supersaccharin solution (0.125% saccharin and 3% sucrose in water) paired with an intraperitoneal injection of EtOH (0, 1, 1.25, 1.5 or 1.75 g/kg). This cycle was repeated every other day for 3 more sessions, providing the opportunity to track emergence of CTA over days. Water pre-exposed males showed significant CTA at 1 g/kg and higher, whereas significant CTA did not emerge in EtOH- exposed males until a dose of 1.5 g/kg and above. Females, in contrast showed significant CTA beginning at 1.25 g/kg regardless of prenatal exposure condition. We then investigated whether the same prenatal exposure would increase EtOH consumption in adulthood. At the beginning of the dark cycle, pair-housed rats (P56-60) were separated by a wire-mesh divider and each was presented with 3 bottles containing 0, 5 and 10% EtOH for 18 hours (19:15-13:15). Dividers were then removed and water access only was provided. Such 3-bottle access was provided every other day for 3 weekly sessions, with 2 days off between weeks (e.g., a M, W, F schedule). In the first access week, drinking was initiated by using 1% sucrose as the vehicle for all 3 solutions, with a 0.5% sucrose solution used in the second week, and water provided as the vehicle in the final week. Two days following the final 18-hour drinking session, rats were given 30-minute access to all bottles and trunk bloods collected to determine blood EtOH content. Males that were prenatally exposed to EtOH showed a significantly greater preference and intake (g/kg) of the 5% EtOH solution on weeks 2 and 3 than water exposed males, whereas no prenatal exposure effect was observed with the 10% EtOH solution. In

contrast, no intake differences were observed in females. Thus, late gestational exposure to EtOH induces a male-specific attenuation in EtOH's aversive effects, which could contribute to the increases observed in later EtOH consumption.
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**Disclosures: J.K. Gore-Langton:** None. **L.P. Spear:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIAAA P50 AA017823.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

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**Topic:** A.09. Adolescent Development

**Support:** 1R21MH092667-01A1

Pennsylvania State Institute for Neuroscience

**Title:** The role of microglia in comorbidity between adolescent asthma and anxiety

**Authors: *J. I. CAULFIELD**[1], S. A. CAVIGELLI[2]
[1]The Pennsylvania State Univ., University Park, PA; [2]Biobehavioral Hlth., Pennsylvania State Univ., University Park, PA

**Abstract:** Adolescence is a developmental period sensitive to perturbations that can affect adult neuronal and behavioral processes associated with internalizing disorders, like anxiety and depression. Asthma is a common adolescent chronic health challenge, affecting 9% of U.S. adolescents, and often comorbid with anxiety and depression. However, little is known about the neurobehavioral impacts of chronic adolescent asthma. Microglia, the resident immune cells of the brain, become activated in response to peripheral insult, and their over-activation has been implicated in neuropsychiatric disorder development. The mechanism underlying the comorbidity of asthma and internalizing disorders, and the involvement of microglia in this relationship, has not been established. Our lab has developed a BALB/c mouse model for chronic adolescent asthma, individually manipulating two components of allergic asthma: airway inflammation (via repeated exposure to house dust mite extract, HDM) and labored breathing (via repeated exposure to methacholine, MCH). Previously published results from the lab have demonstrated that mice exposed to adolescent labored breathing had significantly higher adult anxiety-related neurobiological and behavioral symptoms than unexposed mice. The present study tested acute effects of airway inflammation and labored breathing on microglia activation,

immune marker expression in brain and peripheral tissue, and corticosterone production. We documented these processes in juveniles (postnatal day [P] 21) and near-adults (P56) at 0, 1, 2, 4, 8, or 24 hours after final asthma treatment (HDM or MCH). Classic pro-inflammatory (*IL-6, TNF-α, IL-1β*) were measured in lung, spleen, and hippocampus, and additional markers for microglia (*Cd11b, Iba-1*) were examined in hippocampus. Finally, corticosteroids were measured from serum and feces. Preliminary evidence indicates that weekly MCH exposure led to elevated *Cd11b* expression (indicative of increased microglial activity) compared to controls. Study results suggest that microglia may be involved in one specific pathway that leads to increased internalizing symptoms with asthma.

**Disclosures: J.I. Caulfield:** None. **S.A. Cavigelli:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.12/C39

**Topic:** A.09. Adolescent Development

**Title:** The role of redox dysregulation in behavior and perineuronal net formation after prenatal stress

**Authors: *P. ABBOTT**[1], H. E. STEVENS[2]
[1]Psychiatry, [2]Univ. of Iowa, Iowa City, IA

**Abstract:** Objective: Our lab seeks to understand mechanisms by which early developmental events increase the risk of psychiatric illness. The purpose of this ongoing study is to determine further whether the effects of prenatal stress behavior, GABAergic neurons, and associated perineuronal nets may involve redox dysregulation.
Background: We have found previously that prenatal stress alters cortical GABAergic interneuron maturation in the postnatal period, as evidenced by shifts in the developmental trajectories of cortical populations. How prenatal stress may affect the maturation of inhibitory neurons in other ways is not clear. The formation of extracellular perineuronal nets (PNNs) around GABAergic neurons has been implicated in regulating developmental plasticity and GABAergic cortical maturation. PNNs and their “protection” of GABAergic neurons are influenced by redox dysregulation, a possible mechanism by which prenatal stress influences the brain. To examine these issues, we measured juvenile and adult behavior and PNN structures in a mouse model of prenatal stress (PS). We targeted one aspect of redox dysregulation, by administering a known antioxidant, N-acetylcysteine (NAC).
Methods: In a cohort of pregnant female CD1 mice, bred to GAD67GFP+/- males, half underwent PS: 45 minutes within a restraining tube three times a day starting at embryonic day 12 (E12), seven days prior to parturition. Mothers and pups were given either normal drinking

water or NAC (2 mg/mL) in drinking water from postpartum to weaning. Offspring were tested on the open field as juveniles and on the 3-chambered social task, elevated plus maze, and open field as adults. Using stereological approaches with immunostaining, we examined GABAergic neurons for the presence and absence of PNN envelopment in medial frontal cortex (mFC). Results: PS resulted in an increase in anxiety and motor inhibition in juveniles and adults, as well as reduced sociability in adults. Our data suggest a partial amelioration of these behavioral changes with postnatal NAC administration. We have found that PS reduces PNN envelopment around GABAergic neurons in juvenile mFC. Stereological counts in the mFC of juvenile NAC exposed animals are ongoing.
Conclusion: The effects of PS on anxiety-like and social behavior may involve redox dysregulation during the postnatal period. PNN formation was reduced in mFC after PS and may also be influenced by postnatal antioxidant administration. Ongoing studies are focused on direct measurement of redox dysregulation in the postnatal brain of our PS model. These studies have translational implications for developing better interventions for psychiatric disorders.

**Disclosures: P. Abbott:** None. **H.E. Stevens:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.13/C40

**Topic:** A.09. Adolescent Development

**Support:** NIH Grant AA017359

**Title:** Estrogen modulates ethanol-induced memory deficit in post-pubertal female rats

**Authors: *R. SIRCAR**[1,2], J. TRAVIS[2]
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**Abstract:** Ethanol impairs memory, particularly hippocampus-related memory functions, in adolescent rats. Most studies in literature have reported ethanol-induced memory deficit in pre-pubertal rats. Here we report the effect of ethanol in post-pubertal male and female adolescent rats. Adolescent rats were administered a single injection of ethanol (2 g/kg) intraperitoneally or equivalent volumes. Female rats were ovariectomized and given hormonal supplementation (estrogen and/or progesterone). Controls included sham-operated and vehicle-treated animals. Rats were trained in the fear conditioning paradigm, and 24h later they were tested for: (i) contextual fear conditioning in the same training chamber, and (ii) cued fear memory in a modified test chamber. Freezing during contextual and cued fear conditioning tasks were recorded, and freezing scores were computed for each animal. Acute ethanol-treatment in intact post-pubertal female rats showed significant disruptions in hippocampus-related contextual

memory but not amygdala-associated cued fear memory. Post-pubertal male rats did not show any ethanol-induced memory deficit. In ovariectomized post-pubertal female rats, exogenously administered estrogen, along with or without progesterone, altered the sensitivity of ethanol-induced memory impairment in. Our data suggests that female gonadal hormones modulate ethanol-induced memory impairment in post-pubertal female animals.

**Disclosures: R. Sircar:** None. **J. Travis:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.14/C41

**Topic:** A.09. Adolescent Development

**Support:** F31 NS100277

**Title:** Environmental enrichment promotes generation of new oligodendrocytes and attenuates hypoxia-induced perinatal white matter injury

**Authors: *T. FORBES**[1], B. JABLONSKA[2], V. GALLO[3]
[1]Children's Natl. Hlth. Syst., Washington, DC; [2]Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington, DC; [3]Ctr. for Neurosci Resesarch, CRI, Children's Natl. Med. Ct, Washington, DC

**Abstract:** Hypoxic damage to the developing brain sustained as a consequence of preterm birth is associated with permanent neurodevelopmental disabilities. This oxygenation failure predisposes preterm infants to white matter (WM) injury and is associated with many anatomical changes, the most distinctive of which is damage to the periventricular WM. This diffuse WM injury results in the loss of glial cells and causes a significant disruption in myelination, which leads to cognitive and behavioral impairments throughout childhood. Here, we focus on utilization of an enriched environment to attenuate the effects of perinatal hypoxia (HX) on WM development.
Environmental enrichment (EE) is a noninvasive combination of social and physical enhancement of surroundings that provides mammals with more complex social interactions, exposure to novel stimuli, and an opportunity for voluntary physical activity. Previous studies demonstrated that the environment affects both neural plasticity and functional recovery after brain injury. Furthermore, social, family, and environmental factors contribute to improved cognitive outcome of premature children. Therefore, the environment plays a crucial role in promoting functional recovery in the CNS, and may play a role in the repair of developing WM after HX injury.
Data obtained using an established rodent model demonstrate that EE ameliorates the effects of

perinatal HX and enhances oligodendrocyte regeneration after injury. Further, EE improved performance on a WM-specific behavioral task. *This project will test the hypothesis that the resultant oligodendrogenesis and behavioral improvement seen following HX and subsequent EE will lead to enhanced myelination.* Control experiments will be performed to determine the relative individual contributions of locomotor activity and increased socialization, as well as an investigation of alternate time-sensitive paradigms of EE to determine whether critical periods of exposure and recovery exist. Further, using genetic manipulation, we will determine if WM-dependent behavioral improvements seen with EE require de novo myelination.
While considerable progress has been made in identifying and modulating the mechanisms involved in premature brain injury, additional research is needed. The proposed study will not only shed light on the cellular and molecular mechanisms of WM injury, but will also aid in the development of new therapeutic approaches for enhancing recovery after early postnatal hypoxic injury during critical periods of neurodevelopment.

**Disclosures:** **T. Forbes:** None. **B. Jablonska:** None. **V. Gallo:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.15/C42

**Topic:** A.09. Adolescent Development

**Support:** FRM

**Title:** Prevent the onset of cognitive deficits induced by cannabis abuse during adolescence: Benefits of 5-$HT_6$/mTOR pathway early blockade

**Authors: *C. BECAMEL**, C. BERTHOUX, E. DOUCET, J. BOCKAERT, P. MARIN
Inst. of Functional Genomic, Montpellier, France

**Abstract:** Cannabis is the most commonly abused illicit drug and its consumption by young people has increased for the last decades. Cannabis abuse during adolescence confers an increased risk for developing psychiatric disorders such as schizophrenia, suggesting common pathological mechanisms. Recently, we demonstrated that activation of mTOR by prefrontal 5-$HT_6$ receptors is responsible for cognitive impairments in developmental models of schizophrenia. In line with these findings and the role of mTOR in the amnesic-like effects induced by acute administration of Δ9-tetrahydrocannabinol (THC), we hypothesized that non-physiological mTOR activation might likewise underlie cognitive impairments in cannabis abusers during adolescence.
Here, we characterized the role of the 5-HT6-mTOR pathway in the perturbations of cortical synaptic transmission and associated cognitive deficits elicited in a model of chronic-THC

consumption during adolescence. We also explored whether blocking 5-HT6 receptor-elicited mTOR activation during adolescence could be used as disease modifier to prevent the onset of cognitive deficits caused by perturbations of neural development at a critical period of adolescence in abusers of cannabis.Our results show an increased mTOR activity in the prefrontal cortex, in mice injected chronically with THC during adolescence. Moreover, administration of a 5-HT6 antagonist during adolescence abolishes this non-physiological mTOR activation at the adult stage. The balance of excitatory and inhibitory synaptic transmission and the intrinsic neuronal properties are also altered in THC-injected mice compared to controls. Again, administration of a 5-HT6 antagonist during adolescence prevents these alterations. Correspondingly, the deficit in novel object recognition and sociability observed in THC-injected mice was also prevented by administration of a $5\text{-HT}_6$ antagonist during adolescence. Collectively, these results indicate that blocking the $5\text{-HT}_6$/mTOR pathway, at a critical period of adolescence, prevents the deficits induced by cannabis intake during adolescence. It offers a new perspective for preventing the emergence of cognitive deficits, not only in young cannabis abusers but also in individuals with high risk of developing schizophrenia.

**Disclosures: C. Becamel:** None. **C. Berthoux:** None. **E. Doucet:** None. **J. bockaert:** None. **P. Marin:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.16/C43

**Topic:** A.09. Adolescent Development

**Support:** NIH Grant MH079513

**Title:** Conditioned inhibition as a mechanism for enhancing fear regulation during adolescence

**Authors: *H. C. MEYER**, F. S. LEE
Psychiatry, Weill Cornell Med., New York, NY

**Abstract:** Although fear responses facilitate self-preservation by increasing vigilance and helping an animal avoid potential danger, the inability to regulate fear responses can be maladaptive when it prevents the animal from engaging in other goal-directed activities. Altered fear regulation has been shown to be a key feature of a number of mood disorders including anxiety and post-traumatic stress disorder. Anxiety disorders are highly prevalent in developing populations, with diagnoses peaking during adolescence. Unfortunately, conventional behavioral treatments that are based on the principles of fear extinction learning, such as cognitive behavioral therapy, are ineffective for a notable percentage of the adolescent population. Thus, a better understanding of the development of fear acquisition and regulation is necessary to inform

the advent of behavioral interventions better suited for this period. Previously, our lab has established a “sensitive period” for fear learning during peri-adolescence, during which rapid fluctuations in plasticity result in heightened cued fear that is resistant to extinction. To extend this work, we have recently carried out a series of studies investigating the ontogeny of fear regulation in adolescent mice. Specifically, we exposed mice to a cue predicting the explicit absence of an aversive outcome that develops ‘safe’ properties capable of modulating fear responding through a process referred to as conditioned inhibition. Our data show that adolescent mice (postnatal day/PND 29) exhibit enhanced fear regulation (i.e., a reduction in freezing behavior) relative to adult mice when exposed to a ‘safe’ cue, despite similar responding to a distinct ‘fear’ cue that had previously been paired with a footshock. Moreover, when mice were exposed to a compound presentation of both cues, levels of freezing relative to those observed during the ‘fear’ cue alone were reduced to a greater extent in adolescents than adults. These data suggest that exposure to cues that facilitate fear regulation during adolescence may have benefits beyond those seen in adults, an effect that may be mediated by the heightened plasticity in fear circuitry during this sensitive period. Our lab has also previously shown a window of contextual fear suppression specifically during adolescence. The present data replicate this finding and indicate a potential interaction between contextual fear and the efficacy of learning about cues in service of fear regulation.

**Disclosures: H.C. Meyer:** None. **F.S. Lee:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.17/C44

**Topic:** A.09. Adolescent Development

**Support:** Sub-award from Institute for Integration of Medicine and Science UL1RR025767

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**Title:** Impact of juvenile cannabinoid receptor targeting on adult restrictive-repetitive behaviors and cytokine expression

**Authors: C. AMAYA**[1], M. LEONARD[1], L. FERREIRA[2], N. A. WITT[2], H. XIA[3], S. T. SCHULTZ[2], *G. G. GOULD[2]
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**Abstract:** Restrictive-repetitive behaviors are a core autism symptom that can be modeled in mice for behavioral pharmacology studies. Marble burying is an index of repetitive behavior that is sensitive to sedatives. In prior studies, administration of WIN55,212-2 (0.1 mg/kg), a cannabinoid receptor ($CB_1$ and $CB_2$) agonist, attenuated burying. Yet marble burying captures only “lower order” repetition, paralleling stereotopies like repetitive movements or manipulation of objects. To examine higher order restrictive “perseverative” behaviors such as insistence on sameness (narrow interests), cognitive flexibility or “reversal learning” tests provide more insight. The water T-maze for mice is modified approach to measure potential efficacy of therapeutics to this end. The test is for a position habit reinforced by successfully locating a platform to escape from water. Following acquisition, the platform position is changed to assess reversal learning. Since the $CB_1$ agonist WIN 55,212-2 acutely suppressed burying, we hypothesized targeting $CB_1$ and/or $CB_2$ receptors in adolescence might persistently alter burying and reversal learning. We compared effects of juvenile sub-chronic exposures to cannabinoid agonists, inverse agonists, and fatty acid amid hydrolase (FAAH) inhibitors in water T-maze and marble burying in adulthood. We found the cannabinoid agonist WIN 55,212-2 delayed habit acquisition. Mice administered FAAH inhibitors such as URB597 or AM404 (a product of acetaminophen metabolism) exhibited delays in reversal, with no reduction in burying. Treatment with the CB1 inverse-agonist AM251 accelerated reversal. In a pilot study, serum collected after behavior was used for cytokine measures using a Biorad Bio-plex mouse cytokine 23-plex panel. Eotxain levels, which inhibit neurogenesis, were high in C57BL6 treated as juveniles with >100 mg/kg acetaminophen. These mice also had elevated TNFalpha and G-CSF, which act as granulocyte stimulation factors. By contrast eotaxin levels were low and along with G-CSF unaffected by acetaminophen, while TNFalpha expression was reduced in acetaminophen treated BTBR mice relative to controls. Studies to determine if these effects can be diminished by adipose derived mesenchymal stem cell treatments are ongoing.
The views expressed are those of the [author(s)] [presenter(s)] and do not reflect the official views or policy of the Department of Defense or its Components. The experiments reported herein were conducted according to the principles set forth in the National Institute of Health. Publication No. 80-23, Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966m as amended.

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**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.18/C45

**Topic:** A.09. Adolescent Development

**Support:** NIH Grant R21 DA040228

NIDA Grant T32 DA017637

**Title:** Maternal nicotine exposure elicits multigenerational nicotine preference and sex-specific behavioral anomalies in adolescent mice

**Authors: *J. M. BUCK**[1], H. C. O'NEILL[2], J. A. STITZEL[3]
[1]Integrative Physiol. and Neuroscience; Inst. for Behavioral Genet., Univ. of Colorado Boulder, Boulder, CO; [3]Inst. Behav Genet., [2]Univ. of Colorado Boulder Inst. for Behavioral Genet., Boulder, CO

**Abstract:** Approximately 10% of pregnant women smoke during the third trimester, and maternal smoking during pregnancy is associated with pre-mature birth, low birth weight, and neuropsychological abnormalities such as ADHD. The present research addresses a void in the literature concerning the multigenerational effects of maternal nicotine (NIC) exposure on locomotor activity and anxiety-like behaviors before, during, and after voluntary NIC consumption in adolescent mice. To model persistent maternal NIC intake preceding and during pregnancy, female C57BL/6J mice (F0) were exposed to NIC (200 µg/mL) in drinking water beginning thirty days prior to mating with a NIC-naïve male and continuing throughout pregnancy and pre-weaning of offspring. F1 generation offspring were subsequently mated to obtain an F2 generation of the NIC-exposed maternal line. The four-bottle choice test (FBCT) was conducted during adolescence in an activity-monitoring home cage (HC) apparatus to assess NIC preference at 0, 25, 50, and 100 µg/mL and to measure baseline (BL) and NIC-induced activity differences between F1 and F2 mice and relative to NIC-naïve (VEH) mice. Acute locomotor activity in a novel environment and anxiety-like behaviors were also assessed via the Open Field test (OFT) at BL and both prior to and following a 24-hour withdrawal (WD) period. Results from the FBCT imply a predisposition to NIC consumption in F1 and F2 generation offspring, coupled with NIC concentration-dependent generational differences in NIC preference. Both F1 and F2 mice consume significantly more NIC than VEH. F1 mice do not display differential NIC preference for any concentration tested. Conversely, F2 mice exhibit significantly greater preference for the 25 µg/mL NIC concentration relative to F1 and VEH, but were comparable to F1 at 50 µg/mL and to VEH at 100 µg/mL. Activity-monitoring data collected during the FBCT indicate sex-specific differences in HC activity and circadian rhythmicity at BL and during NIC consumption and WD. F2 mice display sensitization to the locomotor-activating effects of voluntary NIC intake in the OFT that is absent in F1, suggesting NIC-induced generational differences in acute locomotor response to a novel environment. Analysis of anxiety-like behaviors is ongoing. Taken together, our data suggest that maternal NIC exposure confers increased NIC preference in F1 and F2 generations, coupled with BL and NIC-induced differences in locomotor activity in familiar and novel environments. These findings warrant further research to delineate putative epigenetic mechanisms underlying the multigenerational effects of maternal NIC exposure on NIC intake and activity.

**Disclosures:** **J.M. Buck:** None. **H.C. O'Neill:** None. **J.A. Stitzel:** None.

**Poster**

**464. Animal Models of Brain: Environment Interactions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 464.19/C46

**Topic:** A.09. Adolescent Development

**Support:** New York Research Foundation [Q0942016]

National Institute of Health [ROIHD70888]

**Title:** Chronic Methylphenidate exposure in adolescent rats promotes reversible decreases in [3H] MK-801 binding

**Authors: *K. JALLOH**[1], J. HAMILTON[1], M. HADJIARGYROU[2], D. KOMATSU[3], P. THANOS[1]
[1]Res. Inst. On Addictions, Buffalo, NY; [2]New York Inst. of Technol., Old Westbury, NY; [3]Stony Brook Univ., Stony Brook, NY

**Abstract: Abstract**
Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder affecting approximately 11% of children in the US (Center for Disease Control and Prevention [CDC], 2011). Methylphenidate (MP; Ritalin) is a widely used medication to treat children with ADHD. However, the long-term effects of MP treatment during adolescence is poorly characterized in the literature. The aim of this study is to determine the effects of chronic exposure to MP on the NMDA glutamate receptor. To do this, we employed a previous established drinking paradigm that has been shown to deliver MP doses similar to those seen in patients treated for ADHD (Thanos et al., 2015). Briefly, Sprague-Dawley rats were divided into three treatment groups with voluntary access to either water, low dose (LD) MP, or high dose (HD) MP. 4 mg/kg MP (LD) and 30 mg/kg (HD) were used during the first hour of access (09:00-10:00) and 10mg/kg (LD) or 60mg/kg (HD) were used for remaining seven hours (10:00-17:00). Immediately following a 3-month period of treatment, half of these rats were sacrificed and the remaining half went through an additional 4-week abstinence period before they were sacrificed. In vitro autoradiography was carried out with [3H] MK801 to examine NMDA receptor expression in the brain. Immediately following treatment, the HD MP group showed decreases in [3H] MK-801 binding compared to the water group in the Rhinal (39.5%), Piriform (30.4%), Auditory (34.6%), Visual (13.1%), Amygdala (34.1%) and Hippocampus (34.9%). In addition, differences between the LD and HD groups were found in various cortical and subcortical regions. These effects were short-lived, as no differences between treatment groups were seen following 4 weeks of abstinence. The results of the current study demonstrate the powerful, but reversible effects of long-term MP use on the glutamate system in the brain.

**Disclosures:** **K. Jalloh:** None. **J. Hamilton:** None. **M. Hadjiargyrou:** None. **D. Komatsu:** None. **P. Thanos:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.01/C47

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** COGNITO (Innovation fund, Denmark)

Lundbeck Foundation

**Title:** Alpha7 nicotinic acetylcholine receptor silent agonists, but not agonists, reduce LPS-induced TNF-alpha release from primary microglia cells

**Authors:** ***J. D. MIKKELSEN**, M. SØRENSEN, L. PINBORG
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**Abstract:** The penta-homomeric alpha7 nicotinic acetylcholine receptor (nAChR) is a ligand-gated ion-channel, and activation of the receptor leads to inward flow of calcium and natrium. It is considered that the receptor also signal via other intracellular signaling pathways, and that this is mediated via another receptor mechanism. It has been shown that a subset of alpha7 nAChR modulators such as NS6740 and GTS-21 activate the receptor through a calcium-independent metabotropic mechanism. These are partial agonists, and are both characterized to be acting at very low efficacy and therefore termed silent agonists. Previous studies carried out in THP-1 or Jurkat cell lines, conveys anti-inflammatory properties by reducing the inflammatory cytokine releases after stimulation with these alpha7 nAChR silent agonists. In this study, we characterized the pharmacology of the alpha7 nAChR in cultured primary rat and human microglial cells. The human cells were isolated from neurosurgical temporal cortex samples. We could confirm the anti-inflammatory effects of the silent agonists NS6740 and GTS-21 in human and rat cells. Both compounds reduced a lipopolysaccharide (LPS)-induced TNF-alpha release in cultured primary human microglial cells significantly at concentrations of 30 uM, and full effect was achieved at 100 uM of both compounds. By contrast, full and more efficacious partial agonists such as acetylcholine, nicotine and SSR180791 had no effect. Furthermore, the effects could not be blocked by co-administration of MLA. Notably, NS6740 found to be active in our studies also induce non-conducting conformational states of the receptor, and effects in pain models, but the precise mechanisms of receptor modulation and downstream signaling by NS6740 remain unknown.

**Disclosures:** **J.D. Mikkelsen:** None. **M. Sørensen:** None. **L. Pinborg:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.02/C48

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** NIH Grant 1R21DA03383

HHMI BDSI

Lehigh University Mountaintop

Lehigh University College of Arts and Sciences

Lehigh University Department of Biological Sciences

Lehigh University Accelerator/PA Cure

R44 DA032464

**Title:** Exploring the role of lynx2, a cholinergic modulator, in anxiety mechanisms: A mouse to human correlative study

**Authors: *K. R. ANDERSON**, H. WANG, J. M. MIWA
Biol. Sci., Lehigh Univ., Bethlehem, PA

**Abstract:** It is estimated that 18% of the US adult population are suffering with an anxiety disorder and that only one third of these individuals are receiving any kind of treatment. Even though anxiety disorders are the most common mental illness, they are misunderstood and sufferers often go without treatment, leading to costly medical bills to treat associated illnesses/symptoms and a lower quality of life. Most current anxiety treatments are sedative based or anti-depressants, which only mask the symptoms instead of treating the cause. Although the brain regions associated with anxiety and some underlying mechanisms have been identified, these findings do not address the entire need. To address the cause, it will be necessary to understand the biological underpinnings of anxiety dysregulation.
There is evidence that anxious patients may try to self-medicate through the intake of nicotine, which targets the nicotinic acetylcholine receptors (nAChRs) of the cholinergic system. Specific nAChR subtypes have been implicated in regulating the network excitability of the amygdala, the brain region widely implicated as the mediator of the emotional output of fear and anxiety phenotypes across species. Cholinergic modulation, therefore, is a mechanism for the investigation of anxiolytic strategies. To untangle the role of the cholinergic system we are studying the role of a cholinergic modulator, lynx2. The lynx2 protein binds to and suppresses to

nAChRs in the amygdala and subsequent removal of the lynx2 gene increases baseline anxiety-like behaviors across several paradigms (light-dark assay, elevated plus maze, social interaction test).
We hypothesize that lynx2 modulation of anxiety circuits underlies anxiety regulation. To address this, we are pairing behavioral pharmacology assays and electrophysiology to study anxiety behaviors such as fear extinction. Functional comparative studies are in progress to understand how the knowledge of lynx2 functioning in the mouse anxiety-like behaviors can be applied to humans. We hypothesize further investigation into lynx2 and cholinergic pathway modulation can aid in understanding the biological basis of anxiety.

**Disclosures: K.R. Anderson:** None. **H. Wang:** None. **J.M. Miwa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ophidion.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.03/C49

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** NIH Grant R01 GM103801

NIH Grant P01 GM48677

Barrow Neurological Foundation

**Title:** α-Conotoxin antagonism extended to subunit interfaces outside of conventional nicotinic acetylcholine receptor agonist binding sites

**Authors: *B. EATON**[1], S. CHRISTENSEN[2], J. MCINTOSH[2,4,3], P. WHITEAKER[1]
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**Abstract:** α-Conotoxins (α-Ctxs) have demonstrated exceptional selectivity between subtypes of nicotinic acetylcholine receptors (nAChR), making them invaluable research reagents. α-Ctxs identified to date have exhibited competitive antagonist activity, binding to orthosteric agonist sites located at nAChR subunit interfaces. However, many features of agonist binding interfaces are conserved at the other subunit interfaces within the nAChR assembly. We therefore sought to determine if novel α-Ctxs could antagonize nAChR function by binding outside of conventionally-recognized agonist binding interfaces. First, a library of 460 α-Ctxs was screened *in vitro* using $^{86}Rb^{+}$ efflux to measure function of nAChR populations that were heterologously

expressed in SH-EP1 cells. The abilities of candidate α-Ctxs to block carbamylcholine-evoked function of α3β4- and α3β4α5-nAChR (the latter expressed from a fully-concatenated pentameric construct) were compared. α-Ctxs were also screened at SH-EP1 cells expressing α4β2-nAChR, as an initial control to identify off-target activity. A total of 10 α-Ctxs were identified which appeared to preferentially block function of α3β4α5- over α3β4-nAChR. Since α5 subunits do not contribute to traditionally recognized orthosteric agonist sites, this indicated α-Ctx antagonism through non-conventional sites. These initial hits were next subjected to orthogonal testing using two-electrode voltage-clamp electrophysiology. Activity was compared across nAChR with defined $(\alpha3\beta4)_2\beta4$, $(\alpha3\beta4)_2\alpha3$, or $(\alpha3\beta4)_2\alpha5$ subunit stoichiometries, expressed from concatenated nAChR constructs in *Xenopus laevis* oocytes. Of the 10 initial hits, 7 were validated as having isoform-specific selectivity (in some cases greater than ten-fold). All validated hits exhibited nanomolar $K_d$ values (in some cases low-nM). We intend to develop these leads to improve isoform selectivity and determine selectivity across a wider range of non α3β4*-nAChR subtypes. α3β4*- and α5*-nAChR have been extensively implicated in nicotine addiction, somatic signs of withdrawal, and regulation of reward. However, the roles that various isoforms of α3β4*- and α5*-nAChR play remain uncharacterized. Optimized derivatives of the leads described here have the potential to address this important outstanding question. More generally, our findings provide proof of concept for the use of α-Ctxs to identify selectively, and antagonize potently, nAChR subtypes through sites in addition to conventionally-recognized agonist binding interfaces, greatly extending the range of potential *in vitro* and *in vivo* α-Ctx applications.

**Disclosures:** **B. Eaton:** None. **S. Christensen:** None. **J. McIntosh:** None. **P. Whiteaker:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.04/C50

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** FWF Project P19325-B09

**Title:** Nicotinic acetylcholine receptors (nAChR) control the release of norepinephrine in the mouse spinal cord

**Authors: *P. SCHOLZE**, F. GRÖSSL, S. HUCK
Med. Univ. Vienna, Vienna, Austria

**Abstract:** Nicotinic acetylcholine receptors (nAChR) are of obvious clinical interest: In the peripheral nervous system, the receptors are vital for neurotransmission at the neuromuscular

junction and in vegetative ganglia. In the central nervous system nAChRs have been connected with addiction, learning and memory, neurodegeneration and development. In addition nAChRs are known to play an important role in pain processing of noxious stimuli and in neuropathic pain. The precise mechanism of nicotine induced analgesia is unknown, but could possibly be mediated by stimulating norepinephrine (NE) release in the spinal cord.
In the current study we present data on nicotine-induced release of NE in spinal cord slices. Slices were loaded with 3H-NE, placed in superfusion chambers and neurotransmitter release was stimulated using nicotinic agonists and electrical pulses. In wild-type (WT) mice, nicotine induced a TTX and concentration dependent release of 3H-NE with a half maximal outflow at 7 µM. This release was unaffected by the addition of the α7-nAChR-antagonist methyllycaconitin (MLA), but completely blocked by mecamylamine a non-selective nAChR antagonist. In spinal cord slices of β2-knockout mice nicotine induced release was slightly reduced, while slices of β4-knockout mice showed less than 50% of nicotine induced 3H-NE release compared to WT. Release was unaffected in α5- and α7-knockout mice. Electric stimulation trigged neurotransmitter release in WT spinal cord slices to a similar extent as nicotine.
Nicotine induced 3H-NE release from rat spinal cord slices was significantly smaller compared to mice, indicating a clear species difference. NE-outflow after electric stimulation, however, was only slightly smaller in rat than in mouse spinal cord slices.
Finally we studied the subunit composition of nAChRs in the spinal cord. These receptors are made up by 9α and 3β subunits that can assemble into a multitude of different homo- or hetero-pentameric receptors. It is of central importance to know the exact subunit composition, since it determines the pharmacological and biophysical properties of individual receptor subtypes. Solubilized nAChR were labeled with 3H-epibatidine and precipitated using our self-generated highly subunit-specific antibodies. 85% of all receptors were found to contain the subunits α4β2*; 10% α3β4* and the rest α2β2 or α3β2. In β2 knockout animals all receptors contain an α3β4-backbone, with 70% being pure α3β4- receptors and 30% α3α4β4. In β4 knock out animals nearly all receptors were α4β2*- nAChRs.
Our results confirm that both α4β2- and α3β4-containing nAChRs are critical for [3H]-NE release in the mouse spinal cord.

**Disclosures:** **P. Scholze:** None. **F. Grössl:** None. **S. Huck:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.05/C51

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** DGAPA PAPIIT grant-IN-216416

**Title:** Mecamylamine stimulates dorsal raphe serotonergic neurons by increasing glutamate release

**Authors: O. HERNANDEZ**[1], *S. P. MIHAILESCU[2]
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**Abstract:** Mecamylamine (MCM) is a non-specific and non-competitive blocker of nicotinic acetylcholine receptors (nAChRs), originally used as an antihypertensive drug. Previous studies suggested that MCM increases the activity of the brain serotonergic system by stimulating dorsal raphe nucleus (DRN) serotonergic neurons (Mihailescu et al., 1997), by inducing serotonin (5-HT) release (Kenny et al., 2000; Reuben and Clark, 2000) and blocking 5-HT re-uptake (Ma et al., 2006). Animal studies indicated that MCM produces antidepressant effects in rats (Rabenstein et al., 2006). Unfortunately, these laboratory results could not be confirmed by clinical trials in which seorotonin re-uptake inhibitors were associated with mecamylamine (Dunbar 2009) to obtain stronger antidepressant effects. The present study was destined to determine the mechanisms through which MCM increases the firing frequency of 5-HT DRN neurons. Experiments were performed in brain slices obtained from young (19-21 postnatal days) Wistar rats. The electrical activity of 5-HT DRN neurons was recorded using the whole cell patch clamp technique, in both voltage - and current clamp configurations. MCM, bath administered (3 uM), induced an increase of 5-HT DRN neurons firing rate by approx. 30 %, as assessed through intensity-frequency curves. In other experiments, MCM (3 uM) induced a transient (6-8 min) increase in the frequency of 5-HT DRN neuron glutamatergic spontaneous excitatory postsynaptic currents (sEPSCs) by approx. 100 %. This effect was prevented by slice pre-treatment with the glutamate receptor antagonist 6-Ciano-7-nitroquinoxalina-2,3-diona (CNQX, 10 uM). Pre-treatment of slices with the alfa4beta2 nAChRs specific antagonist dihydro-beta-erythroidine (DHbetaE) (0.1 uM) reduced the increase in frequency of glutamatergic sEPSCs induced by MCM to approx. 70%.These results suggest that MCM induces glutamate release in the DRN by stimulating alpha4beta2 nAChRs of glutamatergic terminals. At its turn glutamate induces the increase in firing rate of 5-HT DRN neurons. A similar mechanism explains the increase in firing rate of 5-HT DRN neurons induced by nicotine (Garduño et al., 2012).

**Disclosures: O. Hernandez:** None. **S.P. Mihailescu:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.06/C52

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** LabEx IEC

**Title:** Nicotinic modulation modelling of hierarchal inhibitory circuit control over resting state ultra-slow dynamics in the prefrontal cortex: Application to schizophrenia-related pathology

**Authors: *M. E. ROOY**[1], F. KOUKOULI[2], U. MASKOS[3], B. S. GUTKIN[4]
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**Abstract:** The prefrontal cortex (PFC), key for higher order cognitive processes, exhibits spontaneous activity that is altered in schizophrenia [1]. Cortical acetylcholine (ACh) release modulates PFC activity via nicotinic acetylcholine receptors (nAChRs) [2] specifically expressed within a hierarchical circuit of inhibitory neurons within layer II/III [3]. Parvalbumin (PV) interneurons, expressing α7 nAChRs subunits [2], target pyramidal cells axosomaticaly, exerting divisive effects on their activity. Somatostatin (SOM) interneurons, expressing both α7 and β2 nAChRs subunits [2], target the dendrites of pyramidal cells, exerting substractive inhibition [4]. The α5 nAChRs subunits are expressed only by vasoactive intestinal polypeptide (VIP) interneurons [5], that preferentially inhibit the SOM cells [6]. In vivo two-photon imaging showed that neural activity of PFC in mice is characterized by synchronous ultra-slow fluctuations, with alternating periods of high and low activity [7]. Genetic deletion of specific nAChRs subunits disrupted these ultra-slow fluctuations, leading to changes in synchrony and duration of activity states. Furthermore, mice expressing a human polymorphism in the α5 nAChRs subunits (α5SNP) associated with high risk for nicotine addiction and schizophrenia [8, 9], show reduced spontaneous activity in the PFC that is reversed by nicotine [3]. Using a circuit modeling approach, we studied the roles of distinct GABAergic interneurons in the generation of synchronous ultra-slow fluctuations. In order to study the effects of substractive vs. divisive inhibition on bistable dynamics in the pyramidal neuron, by the SOM and PV interneuron populations respectively, we used population firing rate modelling incorporating both mechanisms [10], and simulated the effects of nAChRs knock outs. With our model, we could fully account for the changes seen in resting state dynamics under the genetic modifications. We further predict that SOM interneurons play dominant role in the changes of activity-state structure seen in mutant mice, and in the restauration of activity to basal levels recorded in α5SNP mice under nicotine application.

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**Disclosures:** **M.E. Rooy:** None. **F. Koukouli:** None. **U. Maskos:** None. **B.S. Gutkin:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.07/C53

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** KTI-18018.2 PFLS-LS

HiQScreen

**Title:** Walking in the chemical space combined with functional study to identify new molecules active at the α7 neuronal nicotinic acetylcholine receptors

**Authors: *S. BERTRAND**[1], T. SCHAER[1], C. DELALANDE[2], K. MEIER[2], D. BERTRAND[1], J.-L. REYMOND[2]
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**Abstract:** The computer guided exploration of the yet unknown chemical space such as the Chemical Universe Database GDB-17 containing all possible small organic molecules up to 17 atoms and its fragment subset FDB-17,[1] is one of the richest tools available today to identify new active molecules for a given target.[2] Extending our previous drug discovery efforts at the α7 nicotinic acetylcholine receptors (nAChRs),[3] we have identified promising regions of the chemical space and refined our virtual screening strategies, in particular focusing on optimizing pharmacological characteristics such as crossing the blood brain barrier and specifically aiming at the modulation of the receptors.
Properties of the promising candidate molecules were then assessed using functional investigations at the human α7 nAChRs expressed in *Xenopus* oocytes by taking advantage of the automated HiClamp system. Evaluation was conducted by first determining that these molecules are deprived of agonistic activity and then by measuring their effects on the responses evoked by low concentrations of acetylcholine using a protocol of irregular receptor stimulation (also referenced as priming). Priming of the α7 receptors is known to correlate with procognitive activity, which suggests that molecules identified with this experimental paradigm should be promising candidates to restore age or disease related cognitive deficits.
The observation that cotinine, the inactive metabolite of nicotine, causes a significant priming at the human α7 nAChRs but is deprived of any agonistic activity provided a further initial condition to adjust the computer screening. We performed a virtual screen of FDB-17 for new analogs of cotinine using fingerprint based similarity, and selected eleven compounds for further characterization based on 3D-shape and pharmacophore based comparisons and commercial availability. Functional testing of these eleven molecules revealed that none of them evoked currents when applied alone at α7 receptors but that five of them caused a significant potentiation (> 1.5 fold) of the response evoked by 40 μM acetylcholine.

Illustrating the power of combination of computer guided exploration of the chemical space and functional studies, these results also demonstrate the possibility to discover novel active molecules at the human α7 nAChRs with pharmacological profiles differing from the currently known compounds.

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**Disclosures: S. Bertrand:** None. **T. Schaer:** None. **C. Delalande:** None. **K. Meier:** None. **D. Bertrand:** None. **J. Reymond:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.08/C54

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** NIH Grant DA035942 (R.M.D.)

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Bernice E. Bumpus Foundation Early Career Innovation Award (Y.K.)

**Title:** Characterization and utilization of PhotoActivatable Nicotine (PA-Nic) for interrogation of the subcellular expression patterns of nicotinic acetylcholine receptors (nAChRs)

**Authors: *M. C. ARVIN**[1], S. BANALA[4], N. M. BANNON[2], X. JIN[1], Y. WANG[1], J. J. MARSHALL[3], K. R. GEE[5], A. CONTRACTOR[3,2], H. A. LESTER[6,4], Y. KOZOROVISKIY[2], R. M. DRENAN[1], L. D. LAVIS[4]
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**Abstract:** Tobacco abuse contributes to several disease states that are estimated to account for >8 million human deaths per year by 2030. The primary reinforcing properties of nicotine are mediated by its actions at neuronal nicotinic acetylcholine receptors (nAChR). The subcellular localization of ion channels is intrinsically tied to their function, and we note that the relationship between nAChR localization and function is a largely uninvestigated aspect of nAChR biology. This is due, in part, to a lack of tools for interrogating the location of functional nAChRs in native systems. To remediate this limitation and expand our understanding of nAChR neurobiology, we developed a photoactivatable nicotine (PA-Nic) molecule. PA-Nic employs an unconventional quaternary ammonium linkage that is chemically stable and elicits a desirable red-shift in absorption maximum. Utilizing patch clamp electrophysiology in acute *ex vivo* mouse brain slices, we show that photochemical uncaging of PA-Nic generates free nicotine in a spatially and temporally controllable manner. We confirm that flash-evoked currents are mediated by nAChRs through mecamylamine inhibition and additional biophysical experiments. By leveraging light-dependent temporal control of nicotine release, we generate photochemical dose-response curves mediated by native nAChRs in the medial habenula (MHb) to interpeduncular nucleus (IPN) circuit, a critical pathway that modulates nicotine addiction and withdrawal. Flash-evoked photochemical dose-response curves suggest the main effect of chronic nicotine is to increase the total number of functional surface receptors, without influencing the potency of nicotine at those receptors. Using 2-photon laser scanning microscopy and laser flash photolysis, we demonstrate that spatially selective PA-Nic uncaging elicits nAChR currents at distinct subcellular locales. MHb neurons expressed nAChRs in most subcellular locations, but interestingly, these neurons may exhibit preferential surface expression near the soma and proximal dendritic segment relative to distal dendrites. Uncaging responses were enhanced on somata and dendritic processes of neurons from mice exposed to chronic nicotine, suggesting that chronic nicotine may sensitize MHb neurons to nicotine or cholinergic input via multiple cellular mechanisms. Finally, we find that PA-Nic is useful in 2-photon photolysis, suggesting this probe could be used to precisely localize nAChRs at discrete cellular locations. In summary, PA-Nic is a versatile and useful new probe for examining nAChR functional activity, likely enabling new discoveries pertaining to cholinergic transmission.

**Disclosures: M.C. Arvin:** None. **S. Banala:** None. **N.M. Bannon:** None. **X. Jin:** None. **Y. Wang:** None. **J.J. Marshall:** None. **K.R. Gee:** None. **A. Contractor:** None. **H.A. Lester:** None. **Y. Kozoroviskiy:** None. **R.M. Drenan:** None. **L.D. Lavis:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.09/C55

**Topic:** B.02. Ligand-Gated Ion Channels

**Title:** Novel α3β2 neuronal nicotinic acetylcholine receptor stable transfection cell line with inducible promoter to change subunit expression ratios

**Authors: *S. N. SUDWEEKS**[1], A. SEGO[2]
[1]Physiol. and Dev. Biol., [2]Neurosci., Brigham Young Univ., Provo, UT

**Abstract:** Nicotinic acetylcholine receptors (nAChR) are found widely throughout the brain both pre- and post-synaptically and participate in a number of physiological functions. Recent research from our lab has shown that α3 and β2 are the most commonly co-expressed nAChR subunit mRNAs in CA1 hippocampal interneurons from the stratum radiatum and stratum oriens, leading us to believe that the α3β2 nAChR is one of the most prevalent nAChR type in these specific interneurons. Recordings from whole cell electrophysiology in Xenopus leavis of the α3β2 nAChR show that there are two distinct α3β2 nAChR subtypes - likely ($(\alpha3)_3(\beta2)_2$ and $(\alpha3)_2(B2)_3$). Given the unique distribution of the α3β2 nAChR, it is worthwhile to explore its role in memory and cognition and as a potential target for pharmaceutical based cognitive therapies. The proposed study is to make an α3β2 stably transfected cell line with a tetracycline (TET) inducible promoter in HEK-293 cells. The TET inducible promotor will allow for quantitative control of the expression ratios between the two subunits such that two likely α3β2 stoichiometries ($(\alpha3)_3(\beta2)_2$ and $(\alpha3)_2(B2)_3$) can be separated and voluntarily induced. This new stably transfected cell line will allow for study and characterization of the α3β2 nAChR in a mammalian environment via whole cell electrophysiology recordings, which will 1) confirm recent α3β2 recordings from Xenopus laevis 2) provide kinetic differentiation amongst the two likely α3β2 stoichiometries and 3) provide a cell line for screening α3β2 targeted cognitive therapies.

**Disclosures: S.N. Sudweeks:** None. **A. Sego:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.10/C56

**Topic:** B.02. Ligand-Gated Ion Channels

**Title:** GTS-21 has cell-specific anti-inflammatory effects that are independent of α7 nicotinic receptors

**Authors: B. K. GARG**, *R. H. LORING
Pharmaceut. Sci., Northeastern Univ., Boston, MA

**Abstract:** GTS-21 is a partial agonist for α7 nicotinic acetylcholine receptors (nAChRs) that is widely used to study the cholinergic anti-inflammatory pathway (e.g. Hilderman et al. *Clin*

*Kidney J.* ***8:***599, 2015 or Norman et al. *J. Neurosci.* ***31:***3446, 2011). However, Nullens et al. (*Shock*. ***45*:**450, 2016) report that GTS-21 is effective in a sepsis model in both wild type (WT) and α7 knockout (α7-KO) mice. To evaluate possible α7-independent anti-inflammatory GTS-21 effects at a molecular level, we investigated two cell lines and macrophages from both WT and α7-KO mice. The first cell line, GH4C1 cells, readily expresses α7 nAChRs when transfected, and respond to the inflammatory cytokine tumor necrosis factor (TNF) when co-transfected with an NFκB-driven alkaline phosphatase (AP) reporter gene (NFκB: Nuclear factor kappa light chain enhancer of B cells, part of a major pro-inflammatory signaling pathway). However, GTS-21 blocks neither TNF-induced phosphorylation of IκB nor AP secretion (both indicators of NFκB activation in these cells). These results suggest that GTS-21 stimulation is insufficient to block TNF-induced inflammatory markers in GH4C1 cells expressing α7 nAChRs. In our hands, the macrophage-like RAW264.7 cell line expresses neither α7 mRNA nor surface α7 nAChRs detected by alpha-bungarotoxin (BGT) binding (See however, Yue et al. *Int. Immunopharmacol*. ***29:*** 504, 2015). 50 μM GTS-21 significantly blocked lipopolysaccharide (LPS)-driven IκB phosphorylation and TNF secretion in RAW264.7 cells, but this latter effect was not prevented by the α7 nAChR antagonists BGT (12.5 μM) or methyllycaconitine (MLA, 10 μM). Finally, mouse WT macrophages express both α7 mRNA and surface BGT binding, while macrophages from α7-KO mice do not. 50 μM GTS-21 significantly blocks both LPS-induced phospho-IκB, and secretion of TNF as well as secretion of the cytokine interleukin-6 in macrophages from both WT and α7-KO mice. A minor fraction of these GTS-21 effects were blocked by BGT and MLA in WT macrophages, but these antagonists had no effect on GTS-21 in α7-KO macrophages. These results suggest that GTS-21 may have different effects on TNF- and LPS-induced inflammatory signaling, and the majority of GTS-21 anti-inflammatory effects are independent of α7 nAChRs in these model systems. Thus, care should be taken interpreting studies using GTS-21 to study α7 nAChR anti-inflammatory effects.

**Disclosures: B.K. Garg:** None. **R.H. Loring:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.11/C57

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** NIGMS RL5GM118990

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NIGMS 1UL1GM118991

**Title:** Levamisole, a positive allosteric modulator for the α3β4 nicotinic acetylcholine receptors prevents weight gain in CD-1 mice on a high fat diet

**Authors: J. A. LEWIS**[1], J. L. YAKEL[2], *A. A. PANDYA[1]
[1]IAC / CRCD, UAF, Fairbanks, AK; [2]Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC

**Abstract:** Neuronal nicotinic acetylcholine receptors (nAChRs) regulate the function of multiple neurotransmitter pathways throughout the central nervous system. This includes nAChRs found on the proopiomelanocortin neurons in the hypothalamus. Activation of these nAChRs by nicotine causes a decrease in the consumption of food in rodents. While nicotine is a non-selective agonist for nAChRs there are other compounds known as Positive Allosteric Modulators (PAMs) that demonstrate selectivity for different nAChR subtypes. In this study we tested the effect of subtype selective allosteric modulators for nAChRs on the body weight of CD-1 mice. Levamisole, an allosteric modulator for the α3β4 subtype of nAChRs, prevented weight gain in mice that were fed a high fat diet. PNU-120596 and desformylflustrabromine were observed to be selective PAMs for the α7 and α4β2 nAChR, respectively. Both of these compounds failed to prevent weight gain in the CD-1 mice. These results suggest that the modulation of hypothalamic α3β4 nAChRs is an important factor in regulating food intake, and the PAMs for these receptors need further investigation as potential therapeutic agents for controlling weight gain.

**Disclosures: J.A. Lewis:** None. **J.L. Yakel:** None. **A.A. Pandya:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.12/C58

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** VA Foundation for Healthy Youth

**Title:** α7 nAChRs regulate the cytoskeleton through calcium-activated calpain

**Authors: *J. KING**[1], E. K. BAK, 22030[1], N. KABBANI[2]
[1]George Mason Univ., Fairfax, VA; [2]Mol. Neurosci, Krasnow Inst., Fairfax, VA

**Abstract:** α7 nicotinic acetylcholine receptors (α7 nAChRs) are abundant in the mammalian nervous system and play an important role in regulating the structure and function of synapses in development and adulthood. The α7 nAChR has a high permeability to extracellular calcium and can promote the release of intracellular calcium from local ER stores through both ionotropic and metabotropic signaling. Studies show that ligand activation of the α7 nAChR can direct

cytoskeletal assembly in both pre- and postsynaptic compartments. Here we show that stimulation of the α7 nAChR fosters rapid microfilament disassembly via calcium driven calpain cleavage of spectrin at the growth cone. α7 nAChR mediated calpain activation attenuates microtubule elongation at the growth cone leading to changes in neurite outgrowth and branching. These studies reveal a novel role for α7 nAChR mediated calcium signaling via calpain activity in cytoskeletal growth and in the developing nervous system with implications for the treatment of various neurodegenerative diseases.

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

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

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**Program#/Poster#:** 465.13/C59

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** Faculty Development Fund of Texas A&M Health Sciences Center (A.K.H)

**Title:** The antinociceptive effects of desformylflustrabromine in rat model of acute pain

**Authors: F. DEBA**, M. K. VANNOY, S. L. PETERSON, *A. K. HAMOUDA
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**Abstract:** Neuronal nicotinic acetylcholine receptors (nAChRs), especially the α4β2 and α7 subtypes, are expressed in pain transmission pathways and involved in the pathophysiology of neuropathic and inflammatory pains. As such, nAChR-based therapeutics represents a potential strategy to alleviate pain while avoiding the high abuse liability associated with opioid analgesics. To this end, the antinociceptive effects of nonselective nAChR agonists as well as agonists/allosteric modulators selective for α4β2 or α7 nAChR have been demonstrated in a wide range of preclinical and clinical models of pain. In this study, we examine the antinociceptive effects of desformylflustrabromine (dFBr), a naturally occurring positive allosteric modulator of α4β2 nAChR, in *in vivo* rat model of acute pain. Hot-plate and tail-flick nociceptive responses and electronic von Frey anesthesiometer were used to measure the ability of dFBr to increase latency to thermal and mechanical sensitivity, respectively. Intraperitoneal injection of dFBr dose-dependently increased time for hind paw-licking behavior in hot-plate test (~300% at 20 mg/kg) and increased mechanical threshold for paw withdrawal in the von Frey test. dFBr antinociceptive effect was characterized with a fast onset time and short duration. Following intraperitoneal injection, dFBr maximum antinociceptive effect was achieved within ~30 minutes and animals returned to baseline value in 3-4 hours. Experiments are in progress to evaluate the effect of co-administration of dFBr with nicotinic agonists (e.g. nicotine, choline) or antagonists (e.g. dihydro-β-erythroidine) on thermal and mechanical pain latencies. Additionally, blood,

CSF, and brains were collected to determine systemic and brain dFBr levels following intraperitoneal injection.

**Disclosures: F. Deba:** None. **M.K. Vannoy:** None. **S.L. Peterson:** None. **A.K. Hamouda:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.14/C60

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** NIH Grant DA036061

**Title:** Region-specific changes in nAChR subunit expression following chronic co-application of nicotine with either (-)-menthol or (±)-menthol in the murine brain

**Authors: *M. J. MULCAHY**[1], S. M. HUARD[1], J. H. WANG[1], H. A. LESTER[2]
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**Abstract:** Nicotinic acetylcholine receptors (nAChRs) are pentameric cation channels that are expressed in the mammalian central nervous system, the peripheral nervous system, and the neuromuscular junction. Eleven neuronal nAChR subunits have been identified in mammals (α2-7, α9-10, β2-4). Chronic administration of nicotine has been shown to increase the total amount of α4 and β2 subunits in specific brain regions. Menthol is a common cigarette flavoring added to tobacco products as either (-)-menthol or (±)-menthol. We investigated the effect of chronic nicotine, and nicotine co-administered with either (-)-menthol or (±)-menthol in several previously uninvestigated murine brain regions for changes in total β2 nAChR subunit protein expression using western blot analysis. Absence of β2 immunoreactivity was confirmed in both β2 knockout and α4 knockout mice. Male C57bl/6 mice were separated into four treatment groups, vehicle (ethanol), nicotine (2mg/kg/hr) in vehicle, nicotine + (±)-menthol (2mg/kg/hr), and nicotine + (-)-menthol (2 mg/kg/hr) administered via osmotic minipumps for 12 days. In most of the brain regions evaluated, β2 nAChR subunit expression was increased following chronic nicotine. In several regions, co-administration of menthol enhanced β2 nAChR subunit expression over nicotine alone. A comprehensive understanding of upregulation or downregulation of nAChR expression in different brain regions will facilitate our understanding of the effects of nicotine and nicotine + menthol exposure in the mammalian CNS.
**This research was supported by NIH DA036061**

**Disclosures: M.J. Mulcahy:** None. **S.M. Huard:** None. **J.H. Wang:** None. **H.A. Lester:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.15/C61

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** NSERC Discovery Grant

Canada Foundation for Innovation

**Title:** Neurosteroid modulation of α4β2* nicotinic acetylcholine receptors in the prefrontal cortex

**Authors: *B. Y. CHUNG**, C. D. C. BAILEY
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**Abstract:** Acetylcholine (ACh) modulation of neurotransmission within the medial prefrontal cortex (mPFC) is important for higher-order cognitive functions including attention and working memory. This role for ACh is met in part through the activation of α4β2* nicotinic acetylcholine receptors (nAChRs) that are present on pyramidal neurons within layer VI of the mPFC. The neurosteroid 3α-hydroxy-5α-pregnan-20-one (3α,5α-THP, allopregnanolone) is produced *de novo* in the brain in response to acute stress. While it is well-known that 3α-5α-THP provides anxiolytic action by potentiating the function of gamma-aminobutyric acid type A ($GABA_A$) receptors, studies in reduced preparations suggest that it also negatively modulates the function of α4β2* nAChRs. Since ACh neurotransmission within the mPFC supports cognitive functions that may be compromised during stress, we sought to determine whether 3α-5α-THP negatively modulates the function of α4β2* nAChRs within living mPFC layer VI pyramidal neurons. Whole-cell electrophysiology experiments were performed in brain slices prepared from male and female CD1-strain mice at postnatal days 14 to 21. Five-minute exposure to 3α-5α-THP did not affect inward current responses to 1 mM ACh at α4β2* nAChRs on mPFC layer VI neurons. However, a longer 20-minute exposure to 3α-5α-THP significantly inhibited ACh responses in both sexes, with a greater inhibition observed in female mice. This inhibition of ACh action at α4β2* nAChRs persisted in the presence of blockers for GABAergic and glutamatergic signaling. Interestingly, this inhibition was not observed in either sex following 20-minute exposure to the synthetic 3α-5α-THP analogue 3α-hydroxy-3β-methyl-5α-pragnan-20-one (ganaxolone), suggesting that 3α-5α-THP may act indirectly at α4β2* nAChRs in brain slice following back-conversion to the neuroactive intermediate 5α-pregnan-3,20-dione (5α-DHP). Ongoing experiments aim to determine and characterize specific entities within the 3α-5α-THP synthesis pathway that directly inhibit the function of α4β2* nAChRs in our experimental preparation. Results from this study demonstrate that stress-induced neuroactive steroids within the 3α-5α-THP synthesis pathway negatively modulate α4β2* nAChRs on mPFC layer VI

neurons, which may disrupt the critical role for these neurons to support normal cognitive function during periods of stress.

**Disclosures: B.Y. Chung:** None. **C.D.C. Bailey:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.16/C62

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** EC Human Brain Project

INCa Tabac

Institut Pasteur PPU

**Title:** A hierarchy of interneuronal nicotinic receptors in mouse prefrontal cortex and ultra-slow fluctuations

**Authors: F. KOUKOULI**[1], M. E. ROOY[4], J.-P. CHANGEUX[2], *U. MASKOS[3]
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**Abstract:** The prefrontal cortex (PFC) underlies higher cognitive processes that are modulated by cholinergic inputs largely via nicotinic acetylcholine receptors (nAChRs). This brain region exhibits spontaneous activity, which is altered in neuropsychiatric disorders, such as schizophrenia. Human genetic studies have highlighted the polymorphic nature of specific nAChR genes that increase risk for smoking and schizophrenia. Using *in vivo* two-photon imaging, CRISPR/Cas9 technology and pharmacological interventions in the PFC of awake mice, we show that different nAChR subunits control spontaneous PFC activity through a hierarchical inhibitory circuit. Specifically, in mice expressing the human α5 SNP associated with nicotine addiction and schizophrenia and α5 knockout (KO) mice, lower activity of vasoactive intestinal polypeptide (VIP) interneurons resulted in an increased somatostatin (SOM) interneuron inhibitory drive over layer II/III pyramidal neurons. Chronic nicotine administration reverses the hypofrontality observed in α5 SNP mice through possible desensitization of β2 subunits in SOM interneurons. Importantly, we show that β2 nAChR subunits play a key role in the generation of ultra-slow fluctuations (USFs) in the PFC and are specifically required for synchronized activity patterns. These USFs are similar to activity described in the human brain, linked to conscious processing. We can show that chronic application of nAChR antagonists disrupts the generation of USFs and mimics the β2 KO phenotype. Interestingly, expression of the A beta peptide, a hallmark of Alzheimer's disease, exerts a similar effect. This work paves

the way towards new therapeutic strategies targeting nicotinic receptors in mental disorders, and shows that the mouse can serve as an experimental model for brain activity previously thought to be human-specific.

**Disclosures:** **F. Koukouli:** None. **M.E. Rooy:** None. **J. Changeux:** None. **U. Maskos:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.17/C63

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** R01 GM103801

P01 GM48677

**Title:** Synthesis of α-conotoxin analogs using non-natural amino acids to selectively target α3β2 nicotinic acetylcholine receptors

**Authors: *A. J. HONE**[1], J. GAJEWIAK[2], J. MCINTOSH[2]
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**Abstract:** The α3β2 nicotinic acetylcholine receptor (nAChR) subtype is expressed by neurons in both the central and peripheral nervous systems of rodents. In the CNS, α3β2-containing receptors are present in medial habenula-interpeduncular tract nuclei, optic tract, and dopaminergic cell bodies in the ventral tegmental area. Peripherally, α3β2 nAChRs are abundant in autonomic ganglia neurons including those found in superior cervical, nodose and intracardiac ganglia. This receptor subtype is also potentially expressed by dorsal root ganglia neurons. However, unequivocal pharmacological identification has been difficult due to the lack of subtype-selective ligands that can distinguish α3β2 from other closely related subtypes particularly α3β4, α6β2β3, and α6β4. We used α-contoxin PeIA as a platform to develop analogs with increased selectivity for α3β2 over α6β2β3 nAChRs. Electrophysiology experiments in *Xenopus laevis* oocytes have shown that native PeIA shows no ability to distinguish between rat α3β2 ($IC_{50}$ = 19 nM) and α6β2β3 ($IC_{50}$ = 17 nM) nAChRs. However, previous structure-function studies have identified positions in PeIA that are critical for selectivity for α3β2 or α6β2β3 nAChRs. Substitution of these critical residues with non-natural amino acids increased the potency and selectivity for α3β2 over α6β2β3 nAChRs expressed in oocytes. Multiple substitutions generated a PeIA analog that showed a ~50-fold increase in potency over the native peptide for inhibition of α3β2 and was ~70-fold more potent on α3β2 than the α6β2β3 subtype. Furthermore, the analog was ~100-fold and ~1,000-fold more selective for α3β2 over α6β4 and

α3β4 subtypes, respectively. This analog may be useful for pharmacologically identifying α3β2 nAChRs in neurons that express multiple closely related subtypes.

**Disclosures: A.J. Hone:** None. **J. Gajewiak:** None. **J. McIntosh:** None.

**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.18/D1

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** T32-NS48039

R01-NS082851

R01-NS052634

**Title:** Characterizing acetylcholine signaling in glioblastoma

**Authors: *E. G. THOMPSON**[1,2], H. SONTHEIMER[3]
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**Abstract:** Primary brain tumors, gliomas, have thus far evaded effective treatment making them a tremendous challenge clinically. This is due in part to the aggressive, invasive nature of glioma cells to infiltrate the surrounding brain tissue away from the main tumor mass, making complete surgical resection impossible. Consequently, efforts to better characterize the unique features of glioma cells could impact the manner in which these tumors are treated, leading to improved prognosis for patients. Interestingly, gliomas are frequently found in supratentorial brain regions that are richly innervated by cholinergic fibers originating in the basal forebrain. However, whether gliomas sense acetylcholine via acetylcholine receptors (AChR) and whether this affects their biology has not been well studied. In this study, we profiled the expression of AChRs in a cohort of glioma samples, including: cell lines, patient-derived xenografts, and resected glioma tissue from 11 patients. Using RT-qPCR we found that all samples expressed both muscarinic and nicotinic AChRs. Stimulation with AChR agonists lead to a robust intracellular calcium increase, suggesting these receptors are functional and could be modulating mechanisms critical in tumor biology, such as migration, invasion, and proliferation. Because intracellular vesicle fusion is known to be a calcium-dependent process, we first investigated whether the calcium increase we observed upon AChR activation could be influencing the release of proteolytic enzymes. The matrix metalloproteinase (MMP) family is a large group of proteases that is collectively capable of degrading all components of the extracellular matrix. Although MMPs are essential enzymes in various physiological processes such as angiogenesis, morphogenesis,

and tissue repair, they are also associated with many pathological conditions including glioma. We found that all glioma samples expressed MMPs and upon stimulation with AChR agonists MMP release was significantly increased compared to controls. We next determined what level of protein regulation was responsible for this increase in MMP release: transcription, translation, and/or vesicle fusion. Finally, we performed invasion assays to determine if the significant increase in MMP release also enhanced the ability of glioma cells to invade through complex matrices. Our studies suggest that acetylcholine signaling is important in glioma biology and may be targeted to affect cell invasion, provided specific agonists can be developed.

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**Poster**

**465. Nicotinic Acetylcholine Receptors: Physiology and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 465.19/D2

**Topic:** G.05. Anxiety Disorders

**Support:** NIH Grant DA017949

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Penn State University Biobehavioral Health Department

Jean Phillips Shibley Endowment

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**Title:** Paternal nicotine exposure transgenerationally alters gene expression in the cholinergic signaling pathway

**Authors: *M. G. KUTLU**[1], R. COLE[2], J. TUMOLO[3], V. V. PARIKH[4], T. J. GOULD[5]
[1]Penn State Univ., University Park, PA; [2]Psychology and Neurosci., [3]Psychology, [4]Psychology & Neurosci., Temple Univ., Philadelphia, PA; [5]Biobehavioral Hlth., Penn State, University Park, PA

**Abstract:** Tobacco use is the leading cause of preventable death in the US as there are established links between smoking and cardiovascular and pulmonary diseases as well as cancers. However numerous studies have also indicated a relationship between smoking and mental health problems such as anxiety and stress disorders. In addition, with the recent developments in genetics, now we know that the effects of substance of abuse are not confined within the same generation but they may be transgenerationally transmitted through epigenetics mechanisms. In light of these developments, we recently investigated the effects of paternal

nicotine exposure on fear learning and memory in subsequent generations where male adult C57BL/6J mice received either chronic nicotine (Nic-Sired group; 28 days, 12.6 mg/kg/d) or chronic saline (Sal-Sired group) exposure. Our results showed that paternal nicotine exposure resulted in augmented fear learning and recovery in the F1 and F2 generations. In addition, paternal nicotine also altered hippocampal cholinergic function. Specifically, we found that the Nic-Sired F1 and F2 generation mice had an altered response to the enhancing effects of acute nicotine on hippocampus-dependent fear learning. Moreover, using electrochemical recordings, we found that paternal nicotine reduced nicotine-evoked acetylcholine release in both ventral and dorsal hippocampus and potassium-evoked acetylcholine release only in the ventral hippocampus in F1 generation mice. In line with these findings, the results of our whole transcriptome RNA-Seq experiment demonstrated that alterations in fear learning and hippocampal cholinergic function were accompanied by changes in ventral hippocampal gene expression in several pathways including the “Choline Synapse” and “MAPK” pathways. Furthermore, we found that in the Nic-Sired group, expression of two genes (*Chrna3* and *Chrnb4*) within the gene cluster that encode α3/α5/β4 nicotinic acetylcholine receptors (nAChRs) was reduced in the ventral hippocampus. However, although the dorsal hippocampus showed expression changes in the genes within the MAPK pathway, we did not find expression changes in the “Choline Synapse” pathway for dorsal hippocampus. Together, our results suggest that paternal nicotine exposure leads to alterations in the hippocampal cholinergic function and expression changes in the associated gene pathways.

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**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.01/D3

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** SFB 746

TP 16

Fa 332/9-1

**Title:** AMPA-receptor specific biogenesis complexes control synaptic transmission and intellectual disability

**Authors: J. SCHWENK**[1], A. BRECHET[1], S. BOUDKKAZI[1], G. ZOLLES[1], W. BILDL[1], A. KULIK[1], U. SCHULTE[1], L. COLLEAUX[2], R. ABOU JAMRA[3], *B. FAKLER[1]

[1]Inst. of Physiol., Freiburg, Germany; [2]INSERM UMR 1163, Inst. IMAGINE, Paris, France; [3]Inst. of Human Genet., Leipzig, Germany

**Abstract:** AMPA-type glutamate receptors (AMPARs) mediate the majority of fast excitatory synaptic transmission in the CNS. They are macromolecular complexes composed of GluA1-4 proteins, the pore-forming subunits arranged as tetramers, accompanied by a defined set of interacting proteins. The latter determine properties and cellular functions by modulating gating and membrane trafficking of AMPARs that are key processes for adjusting synaptic efficacy. Here, by using quantitative mass spectrometry we identify AMPAR complexes that transiently form in the endoplasmic reticulum (ER) and lack the core-subunits typical for synaptic AMPARs. Subcellular interactome studies unravel the composition of these ER AMPARs, which contain as central components FRRS1l and CPT1c. These two proteins bind specifically and cooperatively to the pore-forming GluA1-4 proteins. Using in-vitro and in-vivo knock-down experiments, we demonstrate a specific role for these ER complexes in priming the assembly of AMPA receptors and their trafficking to the synapse. The lack of FRRS1l protein by virus-driven deletion impairs (1) the associations of GluA proteins with their inner core subunits TARPs, Cornichons and GSG1l and (2) causes a reduction in the number of AMPARs at synaptic and extra-synaptic sites. In addition, whole exome sequence analysis show that bi-allelic mutations in the human *FRRS1L* gene cause severe intellectual disability with cognitive impairment, speech delay and epileptic activity. Together, our results provide insight into the early biogenesis of AMPARs and demonstrate its pronounced impact on synaptic transmission and brain function.

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**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.02/D4

**Topic:** B.02. Ligand-Gated Ion Channels

**Title:** Functional characterization of the potent AMPA positive allosteric modulator S 47445

**Authors: *S. BRETIN**[1], L. DANOBER[2], T. SCHAER[3], S. BERTRAND[3], D. C. BERTRAND[3]
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**Abstract:** The findings that positive allosteric modulators of the AMPA receptors display procognitive and antidepressant-like effects that would be valuable for the treatment of neurological or psychiatric diseases such as Alzheimer or major depression [1], prompted the

search of new molecules showing enough efficacy and selectivity at these glutamate receptors receptor subtypes. The compound S 47445 showed efficacy in different in vivo animal models assessing cognition or antidepressant/anxiolytic-like effects [2; 3]. Calling for further characterization of the mode of action of S 47445, functional experiments on recombinant human AMPA receptors expressed in *Xenopus* oocytes or mammalian cells were conducted. These experiments revealed without ambiguity that S 47445 acts as a potent positive allosteric modulator at the human AMPA receptors displaying only a modest preference on the multiple receptor subtypes (GluA1/2/4 flip and flop variants). Already efficacious at concentrations as 100 nM, potentiation caused by S 47445 was maintained in presence of repetitive glutamate pulses and showed no reduction over the time frame (30min). Potentiation was observed independently of the expression system (HEK 293 or oocytes) and was associated with an increase of the sensitivity to glutamate, maximal amplitude of the response and reduced receptor desensitization, which are the hallmark of a positive allosteric modulator. Exposure to the negative allosteric modulator GYKI 52466 (from 10 to 100µM) inhibited the potentiation caused by S 47445 (at 1µM) in a concentration dependent manner. Competition experiments revealed, however, that these two molecules are acting at distinct binding site and confirmed the previous results obtained with AMPA/Kainate chimera [4] suggesting that S 47445 binds in the extracellular domain of the AMPA receptors. This drug is currently evaluated in clinical phase 2 studies in Alzheimer's disease patients and in patients with Major depressive disorder.[1] Lynch G (2006) Glutamate-based therapeutic approaches: ampakines. Curr Opin Pharmacol 6:82-88. [2] Louis C et al. Neurodegenerative Dis. 2015; 15(Suppl.1): 1798; [3] S. Bretin et al. Eur. Neuropsychopharmacol. 2015 (Suppl.2): s248-s249.

**Disclosures:** **S. Bretin:** A. Employment/Salary (full or part-time):; Les Laboratoires Servier. **L. Danober:** A. Employment/Salary (full or part-time):; Les Laboratoires Servier. **T. Schaer:** A. Employment/Salary (full or part-time):; HiQScreen. **S. Bertrand:** A. Employment/Salary (full or part-time):; HiQScreen. **D.C. Bertrand:** A. Employment/Salary (full or part-time):; HiQScreen.

**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.03/D5

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** T32GM007464

**Title:** AMPA and kainate receptors differentially modulate navigation in *C. elegans*

**Authors: *P. J. MALDONADO-CATALA**[1], P. BROCKIE[2], J. MELLEM[2], D. MADSEN[2], A. V. MARICQ[2]
[2]Biol., [1]Univ. of Utah, Salt Lake City, UT

**Abstract:** The nematode C. elegans is capable of detecting environmental cues and modifying its behavior accordingly. For example, worms can navigate towards attractive odors and favorable temperatures. The neuronal circuits underlying these behaviors have been identified via cell-ablation studies; however, how the neurons in these circuits modulate navigation towards an attractant is not well understood. The RIA interneurons integrate information from sensory neurons in these circuits and send information to a variety of interneurons and motor neurons. Interestingly, the GLR-3 and GLR-6 kainate subtype of ionotropic glutamate receptors (iGluRs) are exclusively expressed in RIA, which also express the GLR-1 AMPA-type iGluR. Electrophysiological analysis revealed that GLR-3 and GLR-6 form a heteromeric iGluR that is gated by both glutamate and kainate. In addition, the glutamate-gated current mediated by GLR-3 and GLR-6 is distinctly different from the AMPAR-mediated current. Furthermore, *glr-1* and *glr- 3/6* knockout animals show deficits in chemotaxis to the odorants, similar to those observed in worms lacking the RIA interneurons. Here, we show a novel role for AMPA and kainata receptors in the modulation of backwards locomotion during chemotaxis. In addition, our studies reveal a differential role for these receptors in neuronal activation and behavior.

**Disclosures: P.J. Maldonado-Catala:** None. **P. Brockie:** None. **J. Mellem:** None. **D. Madsen:** None. **A.V. Maricq:** None.

**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.04/D6

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** NINDS/NIH

**Title:** FRRS1L associates with dynein vesicles and is critical for glutamatergic synaptic transmission

**Authors: *W. HAN**, H. WANG, J. LI, X. GU, W. LU
NIH/NINDS, Bethesda, MD

**Abstract:** In the mammalian brain, AMPA receptor (AMPAR)-mediated excitatory synaptic transmission is critically regulated by the receptor auxiliary subunits. Recent proteomic studies have identified that Ferric Chelate Reductase 1 Like protein (FRRS1L), whose mutations in human lead to epilepsy, choreoathetosis, and cognitive deficits, is present in native AMPAR complexes in the brain. However, the role of FRRS1L in the regulation of glutamatergic synaptic transmission remains unknown. Here we report that FRRS1L is an integral membrane protein that interacts with GluA1 and GluA2 subunits of AMPARs. In mouse hippocampal neurons, over-expressed FRRS1L partially co-localizes with endogenous GluA1 and primarily localizes at

non-synaptic membranes. Importantly, immunoisolation of neuronal vesicles from mouse hippocampi reveals that FRRS1L is localized at dynein, but not kinesin, vesicles, suggesting that FRRS1L-containing vesicles are primarily transported by the motor protein, especially dynein, in neurons. Functionally, over-expression of FRRS1L does not alter glutamatergic synaptic transmission in CA1 pyramidal neurons in organotypic hippocampal slice cultures. In contrast, CRISPR-based single-cell knockout of FRRS1L strongly reduces neuronal surface and total expression levels of GluA1, and significantly impairs AMPAR-mediated synaptic transmission in mouse hippocampal neurons both in vitro and in vivo. Taken together, these data reveal a unique subcellular distribution of FRRS1L in neurons and demonstrate an important role of FRRS1L in the regulation of excitatory synaptic strength.

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**Poster**

**466. Non-NMDA Receptors**

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**Program#/Poster#:** 466.05/D7

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** NIH Grant EY012141

**Title:** An insensitive kainate receptor mediates reliable signaling in the retina

**Authors: *S. H. DEVRIES**
Northwestern Univ., Chicago, IL

**Abstract: Objective:** Synapses are optimized for efficient communication, but what are the principles of optimization when a single presynaptic terminal has multiple postsynaptic partners with different receptor and contact properties? Here, we describe a synaptic contact between a mammalian cone and the cb1a, one of 5 types of Off bipolar cells. cb1a cells use kainate receptors and make a single contact on a 5 µm diameter cone terminal that is 200-500 nm from the nearest transmitter release sites. We tested whether this synaptic contact is relatively insensitive to released glutamate based on its distance from release sites and found, surprisingly, that sensitivity is further diminished by the expression of an unusual low affinity receptor. **Methods:** We compared the number of vesicles released by a cone to the number detected by a postsynaptic bipolar cell by recording from synaptically connected pairs in voltage clamp in retinal slices. Cone transmitter release was evoked by applying a train of depolarizing pulses from -70 mV and measured by monitoring the anion conductance of the presynaptic glutamate transporter. To obtain glutamate concentration-response curves, the recording pipette was used to slowly withdraw a bipolar cell's soma from the slice leaving behind a tracer filled axon and connected dendrite. Somatic responses to a range of glutamate concentrations (0.22 – 18.0 mM)

were probed by rapid perfusion. Cell types were identified by epifluorescence. AMPA receptors (~20% of the receptors on cb3a/b cells) were blocked with GYKI53655. **Results:** We compared the responses of two Off bipolar cell types, cb1a and cb3a/b, both of which make basal contacts with cones and express UBP310-sensitive kainate receptors. Paired recordings revealed a non-linearity at both the cone to cb3a/b and cb1a cell synapses that followed a power law with exponents of 2.2 ± 0.1 and 3.2 ± 0.4 (n=8 each), respectively. In response to rapid glutamate application, cb3a/b cell receptors had an $EC_{50}$ of 0.37 ± 0.15 mM (n=6), whereas cb1a receptors had an $EC_{50}$ of 1.4 ± 0.4 mM (n=6) or about 4 times higher. **Conclusion:** The combination of distance from release sites and low affinity receptor means that the simultaneous release of at least 3 vesicles from nearby ribbons is required to produce a detectable cb1a cell response. This thresholding will eliminate the noise associated with cone transmitter release at steady voltages which typically involves stochastic sepscs. Only cone membrane depolarizations that result from light absorption will produce coordinate vesicle fusion and responses in cb1a cells. The cone to cb1a cell synapse sacrifices sensitivity for certainty by using a low affinity kainate receptor.

**Disclosures: S.H. DeVries:** None.

**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.06/D8

**Topic:** B.02. Ligand-Gated Ion Channels

**Title:** Förster Resonance Energy Transfer (FRET) analysis of the structural organization of the intracellular domain of homomeric and heteromeric AMPA receptors

**Authors: L. G. DORVIL**[1], A.-S. HAFFNER[3], D. CHOQUET[4], *A. S. KRISTENSEN[2]
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**Abstract:** AMPA receptors (AMPARs) are glutamate-gated cation channels that mediate the majority of fast excitatory neurotransmission in the central nervous system. AMPARs are tetrameric assemblies of GluA1 to GluA4 subunits. Cryo-EM and X-ray crystal structures of homomeric and heteromeric AMPARs has recently been provided; showing a highly modular receptor architecture with an extracellular domain containing four glutamate binding sites coupled to a transmembrane domain containing the central ion channel. AMPARs also contain an intracellular domain (ICD) formed of C-terminals from each subunit. The ICD is important for interactions with intracellular proteins and contains multiple regulatory phosphorylation sites, but the structure and mechanistic role of the ICD is poorly understood; in part because the ICD is not resolved in present structures. We have used a Förster Resonance Energy Transfer (FRET)

approach to study intramolecular distances and dynamics of the ICD in homomeric and heteromeric AMPARs by insertion of fluorescent proteins (FPs) at various intracellular positions in the GluA1 and GluA2 subunits. Using fluorescence life-time imaging (FLIM) to determine FRET efficiencies between FPs in the ICD or a membrane dye, we determine relative distances within the ICD and to the membrane. Furthermore, we investigate the effect of phosphorylation mimicking mutations in the GluA1 subunit on FRET and identify mutation-induced changes that suggest the phosphorylation state of GluA1 C-terminal can change the structure of the ICD.

**Disclosures: L.G. Dorvil:** None. **A. Haffner:** None. **D. Choquet:** None. **A.S. Kristensen:** None.

**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.07/D9

**Topic:** B.02. Ligand-Gated Ion Channels

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**Title:** GluD1 plays a key role in slow glutamatergic transmission in midbrain dopamine neurons

**Authors: *L. TRICOIRE**[1], N. BENAMER[2], F. MARTI[2], R. LUJAN[4], R. HEPP[2], G. FRÉBOURG[3], S. PONS[5], U. MASKOS[5], P. FAURE[2], Y. HAY[2], B. LAMBOLEZ[2]
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**Abstract:** GRID1 gene encodes GluD1, which forms with GluD2 the delta family of ionotropic glutamate receptors. GluDs have remained orphan of a pore-opening ligand since their cloning, raising doubts on their function as ion channels, until the recent demonstration that GluD2

channels opening is triggered by mGlu1 activation through the canonical Gq/phospholipase C/protein kinase C pathway, and plays a key role in slow glutamatergic transmission in the cerebellum. Human mutations of the GRID1 gene are associated with schizophrenia but the explicit role of GluD1 in brain circuits is unknown. GluD1 is localized at the postsynaptic density of excitatory synapses and its expression increases during postnatal development. Based on the known function of its paralog GluD2 in cerebellum, we searched for a role of GluD1 in slow glutamatergic transmission mediated by metabotropic receptor mGlu1 in midbrain dopamine neurons, whose dysfunction is a hallmark of schizophrenia. We found that an mGlu1 agonist elicits a slow depolarizing current in HEK cells co-expressing mGlu1 and GluD1, but not in cells expressing mGlu1 or GluD1 alone. This current is prevented by additional co-expression of a dominant-negative GluD1 dead pore mutant. We then characterized mGlu1-dependent currents in dopamine neurons from midbrain slices. Both the agonist-evoked and the slow postsynaptic currents are abolished by expression of the dominant-negative GluD1 mutant, pointing to the involvement of native GluD1 channels in these currents. Likewise, both mGlu1-dependent currents are suppressed in GRID1 knockout mice, which reportedly display endophenotypes relevant for schizophrenia. Our results deorphanize GluD1, unravel its key role in slow glutamatergic transmission and provide insights into how GRID1 gene alterations can lead to dopaminergic dysfunctions in schizophrenia.

**Disclosures:** **L. Tricoire:** None. **N. Benamer:** None. **F. Marti:** None. **R. lujan:** None. **R. Hepp:** None. **G. Frébourg:** None. **S. Pons:** None. **U. Maskos:** None. **P. Faure:** None. **Y. Hay:** None. **B. lambolez:** None.

**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.08/D10

**Topic:** B.02. Ligand-Gated Ion Channels

**Title:** Bidirectional modulation of heteromeric acid-sensing ion channel 1a/3 channels by zinc

**Authors: *X. CHU**[1], Q. JIANG[2]
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**Abstract:** Acid-sensing ion channels 1a and 3 subunits are expressed in sensory neurons and retina. Here, we found that heteromeric ASIC1a/3 channels expressed in CHO cells, are regulated by physiological concentration of zinc with dual effects. Co-application of zinc dose-dependently potentiates both the peak amplitude and sustained component of heteromeric ASIC1a/3 channel currents, pretreatment with zinc between 3 to 100 μM exerts the same potentiation as co-application. However, pretreatment with zinc induced the significant inhibition

of heteromeric ASIC1a/3 channels when concentration of zinc is over 100 μM. The potentiation of heteromeric ASIC1a/3 channels by zinc is pH-dependent, as zinc shifts the pH-dependences of ASIC1a/3 current from a $pH_{50}$ of 6.5 to 6.9; while the inhibition of ASIC1a/3 currents by zinc is pH-independent. The inhibition of ASIC1a/3 currents by pre-applied zinc was independent of pH activation, steady-state desensitization, voltage, or extracellular $Ca^{2+}$. Further, systemic mutation of histidine residues in extracellular domain of ASIC3, but not ASIC1a subunit abolished the zinc effects on heteromeric ASIC1a/3 channels. These findings suggest that histidines (located in the ASIC3) in the extracellular domain of heteromeric ASIC1a/3 subunit is critical for zinc-mediated effect.

**Disclosures: X. Chu:** None. **Q. Jiang:** None.

**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.09/D11

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** BFU2015-71422-R

**Title:** CMPDA is a novel potent positive allosteric AMPA receptor modulator affecting synaptic transmission and plasticity with distinct effects in SorCS3-deficient hippocampus

**Authors: *M. M. HOLM**[1], B. MORENO-LÓPEZ[2], V. GARCÍA-MORALES[1,2]
[1]Dept. of Biomedicine, Aarhus Univ., Aarhus C, Denmark; [2]Univ. of Cádiz, Cádiz, Spain

**Abstract:** Fine-tuning of excitatory transmission in the brain can be achieved by allosteric modulation. Positive allosteric modulators (PAMs) of AMPA receptors have been shown to improve memory, facilitate synaptic transmission, promote synaptic plasticity and increase BDNF levels. Conversely, there is a risk of tipping the delicate excitatory-inhibitory balance in the brain. We have recently documented that SorCS3 (sortilin-related receptor CNS expressed 3)-deficient synapses display impaired synaptic transmission and plasticity [Breiderhoff et al., 2013, PLoS ONE, Christiansen et al., 2017, Hippocampus]. Consequently, we hypothesized that PAMs may improve SorCS3-deficient synapses.
Here we employed a novel subunit-bridging PAM entitled phenyl-1,4-bis-alkylsulfonamide (CMPDA) [Timm et al., 2011, Molecular Pharmacology]. To analyze the modulator in native synapses, and to test our hypothesis, we prepared acute brain slices (400 μm) from the SorCS3-deficient mouse model [Breiderhoff et al., 2013, PLoS ONE]. We focused on young adult animals (P55 - P65) of both sexes. Field excitatory postsynaptic potentials (fEPSPs) were recorded in CA1 upon Shaffer collateral stimulation and CMPDA was added to standard artificial cerebrospinal fluid (ACSF) and applied by bath perfusion.

0.1 µM CMPDA potentiated fEPSP slopes about 1.9-fold in wild-type and 1.7-fold in knockout. Increasing the concentration to 1 µM potentiated the fEPSP slopes about 3-fold in wild-type and 4.5-fold in knockout compared to baseline. Interestingly, 0.1 µM CMPDA rescued an intermediate frequency protocol (1 x 100 pulses at 50 Hz) more profoundly in knockout, and even promoted a strong long-term potentiation (LTP) protocol (2 x 100 pulses at 100 Hz). Paired stimulations revealed that 1 µM reduced the paired-pulse facilitation at all intervals, while 0.1 µM increased the facilitation selectively at 50 ms, and only in knockout. Intriguingly, 3 µM produced pronounced pathological epileptiform activity, revealing repeated pyramidal cell firing, even upon single stimulations. This was observed as repetitive population spikes measured by recordings in the pyramidal cell body layer.
In summary, CMPDA positively affects synaptic impairments in SorCS3 knockout. The allosteric modulator enhances synaptic transmission and plasticity, but triggers epileptiform activity, even at relatively low concentrations.

**Disclosures: M.M. Holm:** None. **B. Moreno-López:** None. **V. García-Morales:** None.

**Poster**

**466. Non-NMDA Receptors**

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**Topic:** B.02. Ligand-Gated Ion Channels

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**Title:** SynDIG4/Prrt1 is required for excitatory synapse development and plasticity underlying cognitive function

**Authors: *E. DIAZ**[1], L. MATT[1], L. M. KIRK[1], G. CHENAUX[1], D. J. SPECA[1], K. R. PUHGER[2], M. C. PRIDE[2], M. QNEIBI[3], T. HAHAM[3], Y. STERN-BACH[3], J. L. SILVERMAN[2], J. N. CRAWLEY[2], J. W. HELL[1]
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**Abstract:** Altering AMPA receptor (AMPAR) content at synapses is a key mechanism underlying the regulation of synaptic strength during learning and memory. Previous work demonstrated that *SynDIG1* (Synapse Differentiation Induced Gene 1) encodes a transmembrane AMPAR associated protein that regulates excitatory synapse strength and number (Kalashnikova et al., 2010; Chenaux et al., 2016). The related protein SynDIG4 [SD4, also known as Prrt1 (Proline rich transmembrane protein 1)] has been identified as a component of AMPAR complexes. Here we investigate the role of SD4 in excitatory synapse development and function. SD4 modifies AMPAR gating properties in a subunit dependent manner. SD4 slows the deactivation kinetics of both GluA1 homomers and GluA1/2 heteromers and it has a synergistic effect in the presence of TARPγ8. SD4 also reduces the desensitization of GluA1 homomers with or without TARPγ8, but it has no significant effect on the desensitization of heteromeric GluA1/2. SD4 does not alter recovery from desensitization of either GluA1 homomers or GluA1/2 heteromers. Two week old SD4 knockout (KO) mice exhibit reduced miniature excitatory postsynaptic current (mEPSC) amplitude in CA1, which is corroborated by immunocytochemistry, suggesting that loss of SD4 results in weaker synapses. Remarkably, adult SD4 KO mice show complete loss of long-term potentiation (LTP) induced by a single 100 Hz tetanus without a striking reduction in synaptic transmission. Furthermore, SD4 KO mice exhibit deficits in two independent cognitive assays, Morris water maze acquisition and novel object recognition, indicating that loss of SD4 directly impacts higher order circuit function. Previously, we showed that SD4 co-localizes with the AMPAR subunit GluA1 at non-synaptic sites in neurons and brain sections (Kirk et al, 2016), implying that SD4 influences primarily extrasynaptic AMPARs. We propose that SD4 maintains a pool of extrasynaptic AMPARs critical for synaptic potentiation that manifests as altered circuit function in the mature brain. The finding that loss of SD4 abolishes LTP without an impact on synaptic transmission is particularly significant in light of current evidence indicating that an extra/non-synaptic reserve pool of receptors is critical for LTP (Granger et al., 2013), consistent with our hypothesis that SD4 establishes a reserve pool of GluA1-containing AMPARs critical for potentiation.

**Disclosures: E. Diaz:** None. **L. Matt:** None. **L.M. Kirk:** None. **G. Chenaux:** None. **D.J. Speca:** None. **K.R. Puhger:** None. **M.C. Pride:** None. **M. Qneibi:** None. **T. Haham:** None. **Y. Stern-Bach:** None. **J.L. Silverman:** None. **J.N. Crawley:** None. **J.W. Hell:** None.

**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.11/D13

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** National Basic Research Program of China Grant 2014CB942804

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National Science Foundation of China Grant 31371061

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**Title:** Spatial assembly of heteromeric AMPA receptors

**Authors: *Y. SHI**
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**Abstract:** AMPA-type glutamate receptors (AMPARs) mediate fast excitatory neurotransmission and predominantly assemble as heterotetramers in brain. Recently the crystal structures of homotetrameric GluA2 demonstrate AMPARs are assembled with two pairs of conformationally distinct subunits, in a dimer of dimers formation. However, the structure of heteromeric AMPARs remain unclear. Guided by the GluA2 structure, we performed cysteine mutant crosslinking experiments in full-length GluA1/A2 aiming to draw the heteromeric AMPAR architecture. We found the amino-terminal domains (ATDs) determine the first level heterodimer formation. When the dimers further assemble into tetramers, GluA1 and GluA2 subunits have preferred positions, possessing a 1-2-1-2 spatial assembly. By swapping the critical sequences, we surprisingly found that the spatial assembly pattern is controlled by the excisable signal peptides. Replacements with an unrelated GluK2 signal peptide demonstrate that GluA1 signal peptide plays a critical role in determining the spatial priority. Our study thus uncovers the spatial assembly of an important type of glutamate receptors in brain and reveals a novel function of signal peptides.

**Disclosures: Y. Shi:** None.

**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.12/D14

**Topic:** B.02. Ligand-Gated Ion Channels

**Support:** National Basic Research of China Grant 2014CB942804

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**Title:** ABHD6 negatively regulates the surface delivery and synaptic function of AMPA receptors

**Authors: *M. WEI**
Peking Univ., Beijing City, China

**Abstract:** In the brain, AMPA-type glutamate receptors are major postsynaptic receptors at excitatory synapses that mediate fast neurotransmission and synaptic plasticity. ABHD6, a monoacylglycerol lipase, was previously found to be a component of AMPA receptor macromolecular complexes, but its physiological significance in the function of AMPA receptors (AMPARs) has remained unclear. Our study showed that overexpression of ABHD6 in neurons drastically reduced excitatory neurotransmission mediated by AMPA but not by NMDARs at excitatory synapses. Inactivation of ABHD6 expression significantly increased excitatory neurotransmission at excitatory synapses. Interestingly, overexpression of ABHD6 reduced glutamate-induced currents and the surface expression of GluAs in HEK293T cells expressing GluA1-4 and stargazin, suggesting a direct functional interaction between these two proteins. The C-terminal tail of GluAs was required for the binding between of ABHD6 and GluA1. Mutagenesis analysis revealed a short C-terminal sequence in the GluAs that was essential for the inhibitory effect of ABHD6. The hydrolase activity of ABHD6 was not required for the effects of ABHD6 on AMPAR function in either neurons or transfected HEK293T cells. Using CRISPR/Cas9, we generated ABHD6 KO mice. We found that, the surface and total GluA1 expression levels increased significantly in KO mice compared to these of the wt mice. Thus, these findings reveal a novel and unexpected mechanism governing AMPAR trafficking at synapses through ABHD6.

**Disclosures: M. Wei:** None.

**Poster**

**466. Non-NMDA Receptors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 466.13/D15

**Topic:** B.04. Ion Channels

**Support:** NIH Intramural Funding

**Title:** Emergence of circuit and behavioral deficits following conditional AMPAR deletion in CGE-derived interneurons

**Authors: *G. AKGUL**[1], C. J. MCBAIN[2]
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**Abstract:** GABAergic interneurons (INs) critically regulate information flow in the brain and their dysfunction is implicated in many disease states such as epilepsy, schizophrenia and autism. In the hippocampus, they drive early network activity (giant depolarizing potentials, GDP) that is critical for circuit maturation and synchronize pyramidal cell ensembles in adult hippocampus. INs are derived from two progenitor pools located in the ganglionic eminences (CGE and MGE) and migrate to hippocampus during early development. Although MGE-INs have been highly studied, due to the lack of specific genetic tools, characterization of CGE-INs has lagged. Afferent driven recruitment of CGE-INs within local circuits is principally mediated by AMPARs. Here, we examined the role of these receptors in both the maturation and function of CGE-INs in mouse hippocampus during development. To this end, we generated a conditional knockout (KO) mouse that lacks AMPARs selectively in CGE-INs by crossing the 5HT3AR-Cre and floxed-GluA1-GluA2-GluA3 lines. Electrophysiological evaluation in hippocampal slice preparations demonstrated that excitatory synaptic drive onto CGE INs was reduced by 95% in KO mice from neonatal ages through adulthood confirming our genetic knockout strategy. We then probed for potential perturbations in the network activity at both neonatal (P5) and juvenile (P17-21) stages. In KO neonates the GDP frequency was significantly decreased in CA1 hippocampus compared with WTs demonstrating a critical role for AMPAR function in CGE-INs for the coordination of these early network rhythms. In juvenile KO mice, feedforward/feedback inhibition onto CA1 pyramidal cells was significantly impaired when compared to WT. Next we investigated the possible emergence of behavioral abnormalities that may potentially result from these described circuit deficits. In our initial screen, we found that while home cage locomotor activity of adult KO mice was normal, a clear novelty-induced hyperlocomotion and anxiety-like behavior in open-field maze tests was apparent when compared to WTs. In follow up studies, hippocampal dependent behaviors including working memory performance will be assayed using the Morris water maze and T-maze. Taken together our study aims to elucidate the role(s) of AMPARs in the development and maturation of specific cohorts of inhibitory INs and thus may possibly provide new targets for therapeutic treatments for developmental neurological circuit disorders.

**Disclosures:** **G. Akgul:** None. **C.J. McBain:** None.

**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.01/D16

**Topic:** B.04. Ion Channels

**Support:** ERC SINCHAIS

**Title:** Cav2.1 changes its number and relative distribution to the molecular machinery after stimulation in cerebellar parallel fibre-Purkinje cell synapses

**Authors: *H. HARADA**[1], Y. NAKAMURA[2], K. BEPPU[3], K. MATSUI[3], M. WATANABE[4], H. SAKAMOTO[5], S. NAMIKI[5], K. HIROSE[5], R. SHIGEMOTO[1]
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**Abstract:** Vesicular neurotransmitter release at the presynaptic terminal is triggered by activation of voltage-dependent calcium channels (VDCCs). Previous reports have indicated that the precision of vesicular release is determined by the coupling distance between VDCCs and docked vesicles. Another factor which controls the synaptic vesicular release is the molecular machinery consists of membrane-bound proteins, expressed in synaptic vesicles or active zones, which directly/indirectly interact with calcium channels. Although alteration of VDCCs distribution or their association with these presynaptic molecules could contribute to presynaptic plasticity, little is known how they change in an activity-dependent manner. We previously reported that Cav2.1 subunits of P/Q-type calcium channels are concentrated in the presynaptic active zones of parallel fiber-Purkinje cell (PF-PC) synapses, and that they make a few clusters within the active zone. In the present report, we used SDS-digested freeze-fracture replica labeling to examine the distribution patterns of Cav2.1, RIM1/2, Munc13-1, Neurexin and CASK in PF active zone, at steady state condition and optogenetically or physiologically stimulated conditions. At steady state, about 20 immunogold particles for Cav2.1 were found per active zone, making 1-2 clusters with 5-6 particles per cluster. Quantitative analysis using a fitted simulation showed significant co-clustering of Cav2.1 with RIM1/2 and Neurexin but not with CASK. After *in vivo* optogenetic stimulation with a condition that induces long-term depression (LTD) of PF-PC synapses *in vitro*, we found that the number of Cav2.1 significantly decreased just after the stimulation then twice increased 30 min after the stimulation. The distribution pattern of Cav2.1 was modified in a time-dependent manner, whereas the active zone size was not changed. Significant increase in the number of Cav2.1 was also observed after horizontal optokinetic response (HOKR) training in mice and the acrobatic motor skill training in rats. Notably, the increase of Cav2.1 was observed in acute slices both after inducing LTD by optogenetic stimulation and inducing long-term potentiation by Forskolin treatment at PF-PC synapses. The number of Neurexin but not others also increased 30 min after the optogenetic stimulation. The co-clustering and relative distance of RIM1/2, Munc13-1 and Neurexin to Cav2.1 showed differential patterns of activity-dependent change. These results shed light on potential mechanisms underlying the presynaptic plasticity induced by dynamics of VDCCs and their association to presynaptic molecules.

**Disclosures:** **H. Harada:** None. **Y. Nakamura:** None. **K. Beppu:** None. **K. Matsui:** None. **M. Watanabe:** None. **H. Sakamoto:** None. **S. Namiki:** None. **K. Hirose:** None. **R. Shigemoto:** None.

**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.02/D17

**Topic:** B.04. Ion Channels

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**Title:** Molecular basis for CaMKII targeting to an L-type $Ca^{2+}$ channel nanodomain that is required for neuronal excitation-transcription coupling

**Authors: *X. WANG**[1,2], T. L. PERFITT[3], C. R. MARKS[3], S. WANG[4], T. NAKAGAWA[1,3], A. LEE[4,5], D. A. JACOBSON[3], R. J. COLBRAN[1,2,3]
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**Abstract:** Activity-dependent gene transcription is critical for long-term synaptic plasticity and memory formation. Neuronal excitation activates voltage-gated L-type ($Ca_V1.x$) $Ca^{2+}$ channels (LTCCs) in the plasma membrane to initiate a signaling pathway that results in nuclear CREB phosphorylation and immediate early gene expression. Activation of this long-range pathway requires recruitment of $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII) to a nanodomain in the immediate vicinity of the LTCC via an unknown mechanism. Here, we performed a non-biased screen and showed that activated CaMKII strongly interacts with a novel binding motif in the N-terminal domain (NTD) of the $Ca_V1.3$ LTCC α1 subunit that is not conserved in $Ca_V2$ or $Ca_V3$ calcium channels. Mutations in the $Ca_V1.3$ α1 subunit NTD or in the CaMKII catalytic domain that largely prevent the *in vitro* interaction also disrupt CaMKII association with intact

LTCC complexes. Furthermore, these same mutations interfere with excitation-transcription coupling in cultured hippocampal neurons. Lastly, we found that LTCC NTD also interacts with other intracellular components of the calcium channel complex, making it a potential candidate that links voltage-induced channel conformational change to nuclear signaling. Taken together, our findings define a novel molecular interaction with the neuronal LTCC that is critical for the initiation of a long-range signal to the nucleus that is critical for learning and memory.

**Disclosures:** **X. Wang:** None. **T.L. Perfitt:** None. **C.R. Marks:** None. **S. Wang:** None. **T. Nakagawa:** None. **A. Lee:** None. **D.A. Jacobson:** None. **R.J. Colbran:** None.

**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.03/D18

**Topic:** B.04. Ion Channels

**Support:** NIH grant NS055251

**Title:** Epigenetic modification of the CACNA1B gene controls exon choice during splicing of $Ca_V2.2$ pre-mRNA in nociceptors to affect $Ca_V2.2$ channel function in normal and in chronic pain states

**Authors: *E. J. LOPEZ SOTO**[1], D. LIPSCOMBE[2]
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**Abstract:** Tissue-specific alternative processing of precursor mRNAs is a major source of protein diversity in the nervous system. Alternative splicing, a feature of >95% of mammalian genes, is critical for development and function of the nervous system, and it is implicated in a growing number of disorders. We have shown that the selection of one exon over another, during $Ca_V2.2$ pre-mRNA splicing, explains the unique properties of $Ca_V2.2$ channels in nociceptors including their strong sensitivity to inhibition by mu-opioid receptors. We also showed previously that, following nerve injury, the fraction of e37a-containing $Ca_V2.2$ mRNAs in dorsal root ganglia of rat is reduced compared to naïve ganglia, with a concomitant reduction in morphine sensitivity. Here we determine the molecular mechanism that explains cell-specific exon choice at the 37 locus of *CACNA1B*; the $Ca_V2.2$ encoding gene. Contrary to most published examples of splicing, we failed to find a role for a RNA binding protein in e37a splicing, but rather we showed that the multi-zinc finger DNA binding protein CCCTC-binding factor (CTCF) binds in a 60bp region in *CACNA1B* e37a. CTCF is an ubiquitous regulator of DNA in all cells, but it has also been implicated in alternative pre mRNA splicing. Here we present several lines of evidence that CTCF binding within e37a in *CACNA1B* promotes e37a inclusion in $Ca_V2.2$ mRNAs and that its binding is regulated by cell-specific methylation within, or close to e37a of

*CACNA1B*. We found that reduced methylation by a 48 hr treatment with 10 µM of 5-Azacitidine (20.89 ± 2.76 % of control measured by 5-mC DNA ELISA) in the DRG-derived F11 cell line resulted in a 2.02 ± 0.09 fold-increase in e37a expression relative to control. We discovered that DNMT3a, but not DNMT1 or DNMT3b, is the methyltransferase that regulates e37a inclusion. For example, siRNA knock down of DNMT1 did not affect e37a-$Ca_V2.2$ mRNA levels (1.169 ± 0.03 fold of siRNA control). DNMT3a is increased in DRG in peripheral nerve injury models consistent with our findings that e37a levels are reduced in injured but not uninjured DRG, a finding that we repeated using qRT-CPR to quantify e37a levels in mice.

**Disclosures: E.J. Lopez Soto:** None. **D. Lipscombe:** None.

**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.04/D19

**Topic:** B.04. Ion Channels

**Title:** High-throughput chemical screening identifies SGM-45 as a selective inhibitor of N-type voltage-gated (Cav2.2) channels

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**Abstract:** Inhibition of voltage-gated calcium (Cav) channels is a potential therapy for many cardiovascular and neurological diseases. Neuronal Cav1/Cav2 channels are typically composed of α, β and α2δ subunits. The β-subunits of voltage-gated $Ca^{2+}$ channels are cytoplasmic proteins that increase the surface expression of the pore-forming α subunit of $Ca^{2+}$ channels and regulate the biophysical properties of the channel. They do so via a high-affinity protein-protein interaction pocket with the α-subunit of Cavs. Thus, targeting the Cav α-β interaction should result in a new class of calcium channel antagonists with therapeutic potential in nervous system disorders involving dysregulation of calcium. To date, there are no small molecules that physically and selectively disrupt the α-β protein-protein interaction. Here, structure-based virtual screening of a commercial library of 500,000 small molecules docked to the β-subunit led to the identification of 49 compounds. Compound **SGM-45** binds to Cavβ2a, inhibits calcium influx via N-type voltage-gated calcium (Cav2.2) channels reconstituted with different beta subunits (except beta 4) and in rat dorsal root ganglion (DRG) neurons, and is a selective inhibitor of Cav2.2. We also found decreased surface Cav2.2 in DRGs following incubation with **SGM-45**, implicating block of surface expression as a mechanism of action of **SGM-45**. Constellation pharmacology revealed actions of **SGM-45** on a heterogeneous population of

DRGs including those responsive to acetylcholine, mustard oil, ATP, histamine, and capsaicin. Of relevance for pain, we found that **SGM-45** decreases calcium influx during periods of high activity by promoting accumulation of channels in an inactivated state. As certain pain conditions have been associated with hyperexcitability of sensory neurons, it is possible that **SGM-45** could allow for increased accumulation of inactivated Cav2.2 in these neurons. Finally, **SGM-45** reversed mechanical allodynia and thermal hyperalgesia in rats subjected to a plantar incision of the paw, an accepted model of human post-surgical pain. Our study will generate new tools to investigate Cav α-β interactions and underscores the importance of targeting this interaction for development of pain therapeutics.

**Disclosures:** **A. Dórame:** None. **Z. Shuja:** None. **V. Gokhale:** None. **X. Yang:** None. **Y. Ji:** None. **A. Moutal:** None. **Y. Wang:** None. **L.A. Chew:** None. **S.S. Bellampalli:** None. **T.W. Vanderah:** None. **M. Khanna:** None. **H.M. Colecraft:** None. **R. Khanna:** None.

**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.05/D20

**Topic:** B.04. Ion Channels

**Support:** Canadian Institutes of Health Research Operating Funds (RWT)

**Title:** T-type calcium channels associate with FMRP to regulate calcium influx in Purkinje cells

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**Abstract:** Autism Spectrum Disorder (ASD) is characterized by a disorder of synaptic function and plasticity required for normal signal processing, as found in Fragile X syndrome (FXS). In FXS, the expression of Fragile X Mental Retardation Protein (FMRP) is lost, removing its role in regulating mRNA translation of multiple protein targets, including kinases such as CaMKII. Here, we examine the effects of FXS on low voltage-activated T-type (Cav3.1) calcium channels in Purkinje cells and their role in evoking long-term potentiation (LTP) of parallel fiber input. Recordings were made *in vitro* from *wt* mice expressing ChR2 in relation to the L7 promoter in Purkinje cells, and EPSPs selectively evoked postsynaptically by injecting a parallel fiber simulated EPSC at the soma. Delivering a theta burst pattern of light pulses resulted in a rapid LTP of the postsynaptic EPSP that was blocked by the Cav3 channel blockers mibefradil or TTA-P2. Calcium influx restricted to Cav3 channels further promoted phosphorylation of alphaCaMKII in the cytoplasm and CREB in the nucleus, as detected with phospho-specific antibodies. A direct role for CaMKII in Cav3-mediated LTP was shown by a significant

reduction in EPSP potentiation by the CaMKII blocker AIP. We further found that FMRP and Cav3.1 immunolabels colocalize in Purkinje cell somata, and that FMRP coimmunoprecipitates (coIPs) with Cav3.1 channels. Moreover, the coIP between Cav3.1 and FMRP was calcium-dependent in being detected at 0 µM [Ca] (BAPTA), 100 nM [Ca] (neuronal resting [Ca]), and 1 µM [Ca], but lost at 50 µM [Ca]. Infusing an N-terminal active fragment of FMRP in tsA-201 cells expressing Cav3.1 channels invoked a significant hyperpolarizing shift in the voltage-inactivation curve (Vh) that reduced Cav3.1 by ~60% near resting potentials. These data are important in revealing an activity-dependent association between Cav3.1 and FMRP that could enhance Cav3 calcium influx and CaMKII activation during repetitive inputs. We will test the hypothesis that a loss of FMRP in FXS will increase Cav3 calcium influx and CaMKII activation, increasing the probability of LTP that could disrupt signal processing in Purkinje cells.

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**Poster**

**467. Calcium Channel Modulation**

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**Topic:** B.04. Ion Channels

**Support:** NIH R01 NS07892

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NIH R01 HL121059

**Title:** Phosphorylation of $Ca_v1.2$ on S1928 uncouples the L-type $Ca^{2+}$ channel from the beta-2 adrenergic receptor

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**Abstract:** The L-type calcium channel 1.2 (Cav1.2) is the most prevalent LTCC in heart and brain tissue. Cav1.2 forms a complex that includes the beta-2 adrenergic receptor (b2AR), Gs, and AKAP-anchored PKA, allowing for upregulation of channel activity via a Gs-adenylyl cyclase-cAMP-PKA pathway. PKA phosphorylation of residue S1928 on the C-terminus of Cav1.2 is prominently regulated, but its physiological role has not been reported especially in

light of functional studies that argued against a regulatory role in the heart. We have defined here an agonist-triggered downregulation of b2AR that is specific to Cav1.2 in neurons. For local beta-adrenergic regulation of Cav1.2, b2AR binds to residues 1923-1948 of Cav1.2. Phosphorylation of S1928 induced by a b2AR agonist displaced b2AR from Cav1.2, resulting in a refractory period from further beta-adrenergic stimulation. S1928A knock-in mice do not show this refractory period. Although AMPARs also cluster at post-synaptic sites, they do not express these differences in b2AR association and regulation after b2AR stimulation. Hence, this desensitization mechanism by b2AR/cAMP/PKA/S1928 signaling is highly specific to Cav1.2 in the brain. Finally, we found that LTP induced by prolonged theta tetanus (PTT-LTP) depends on Cav1.2 and the b2AR/Cav1.2 association, emphasizing the physiological significance of this agonist-triggered dissociation of b2AR.

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**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.07/D22

**Topic:** B.04. Ion Channels

**Title:** Cdk5 regulates GABA release at striato-nigral terminals by inhibiting L-type calcium channels activity

**Authors: *S. LOYA**[1], M. RODRÍGUEZ[1], R. GONZALEZ[2], A. SANDOVAL[3], R. FÉLIX[3], R. CABALLERO[4], D. ERLIJ[5], B. FLORÁN[1]
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**Abstract:** Neurotransmission is one of the most important processes of neuronal communication that depends largely on calcium movement across ion permeable channels. Cyclin-dependent kinase 5 (cdk5) has been implicated in the regulation of neurotransmission in several studies which suggest that cdk5 exerts a direct regulation on various ion channels. In hippocampal synaptosomes for example, phosphorylation of P/Q type calcium channels prevents its interaction with SNAP25 and synaptotagmin 1, thereby inhibiting glutamate release from these terminals.
In this work, we studied the regulation by cdk5 of presynaptic L-type calcium channels, which regulate significantly the GABA release at striato-nigral terminals (Recillas et al., 2014). Through electrophysiology experiments in slices of substantia nigra pars reticulata (SNr) we

found that, by inhibiting cdk5 with olomoucine (50 μM) there is an increase of high potassium-evoked inhibitory post-synaptic currents (eIPSC) and that this increase can be prevented by adding the specific L-type calcium channel blocker, nifedipine (10 μM). This speaks of an inhibitory mechanism exerted by cdk5 on L-type calcium channels and, according to our previous results, it is due to phosphorylation by cdk5 of a serine residue located at the carboxyl terminus of L-type calcium channels.
Our results suggest a novel mechanism of regulation of neurotransmission at SNr by a phosphorylation event whose knowledge may be useful for the understanding about how GABAergic neurotransmission works and, in the future, for the development of therapeutic alternatives against neurodegenerative diseases such as Parkinson's.

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**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.08/D23

**Topic:** B.04. Ion Channels

**Title:** Homology-guided mutational analysis reveals the functional requirements for antinociceptive specificity of CRMP2-derived peptides targeting N-type voltage-gated (CaV2.2) channels

**Authors: *S. CAI**[1], A. MOUTAL[2], W. LI[2], Y. WANG[2], W. JU[2], S. LUO[2], L. F. MOUTAL[2], S. P. MILLER[2], J. HU[2], E. DUSTRUDE[2], T. VANDERAH[2], V. GOKHALE[2], M. KHANNA[2], R. KHANNA[2]
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**Abstract:** N-type voltage-gated calcium (CaV2.2) channels are critical determinants of increased neuronal excitability and neurotransmission accompanying persistent neuropathic pain. Despite CaV2.2 antagonism being recommended as first-line treatment for neuropathic pain, calcium-current blocking gabapentinoids inadequately alleviate chronic pain symptoms and are often mired by numerous side-effects. Collapsin response mediator protein 2 (CRMP2) targets CaV2.2 to the sensory neuron membrane, and allosterically modulates Cav2.2 functionally. A fifteen amino acid peptide (CBD3), derived from CRMP2, disrupts the functional protein-protein interaction between CRMP2 and CaV2.2 to inhibit calcium influx, transmitter release and acute, inflammatory and neuropathic pain. In this study, we set out to map the minimal domain of CBD3 necessary for its antinociceptive potential. Truncated as well as homology-guided mutant versions of CBD3 were generated and assessed using depolarization-evoked calcium influx in rat dorsal root ganglion (DRG) neurons, binding between CRMP2 and CaV2.2, whole-cell voltage

clamp electrophysiology, and behavioural effects in two models of experimental pain: post-surgical pain and HIV-induced sensory neuropathy induced by the viral glycoprotein 120 (gp120). The first six amino acids within CBD3 accounted for all in vitro activity and antinociception. Spinal administration of a prototypical peptide (TAT-CBD3-L5M) reversed pain behaviours. Homology-guided mutational analyses of these six amino acids identified at least two residues, alanine (at position one) and arginine (at position four), as critical for antinociception in two pain models. These results identify an antinociceptive scaffold core in CBD3 that can be used for development of small-molecule mimetics of CBD3.

**Disclosures: S. Cai:** None. **A. Moutal:** None. **W. Li:** None. **Y. Wang:** None. **W. Ju:** None. **S. luo:** None. **L.F. Moutal:** None. **S.P. Miller:** None. **J. Hu:** None. **E. Dustrude:** None. **T. Vanderah:** None. **V. Gokhale:** None. **M. Khanna:** None. **R. Khanna:** None.

**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.09/D24

**Topic:** B.04. Ion Channels

**Title:** Sustained relief of ongoing experimental neuropathic pain by a CRMP2 peptide aptamer with low abuse potential

**Authors: *L. A. CHEW**[1], J. Y. XIE[2], X. YANG[2], Y. WANG[3], C. QU[2], Y. WANG[2], L. M. FEDERICI[4], S. D. FRITZ[4], M. S. RIPSCH[5], M. R. DUE[6], A. MOUTAL[2], M. KHANNA[2], F. A. WHITE[4], T. W. VANDERAH[2], P. L. JOHNSON[4], F. PORRECA[2], R. KHANNA[2]
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**Abstract:** Uncoupling the protein-protein interaction between collapsin response mediator protein 2 (CRMP2) and N-type voltage-gated calcium channel (CaV2.2) with an allosteric CRMP2-derived peptide (CBD3) is antinociceptive in rodent models of inflammatory and neuropathic pain. We investigated the efficacy, duration of action, abuse potential, and neurobehavioral toxicity of an improved mutant CRMP2 peptide. A homopolyarginine (R9)-conjugated CBD3-A6K (R9-CBD3-A6K) peptide inhibited the CaV2.2-CRMP2 interaction in a concentration-dependent fashion and diminished surface expression of CaV2.2 and depolarization-evoked Ca influx in rat dorsal root ganglia neurons. In vitro studies demonstrated suppression of excitability of small-to-medium diameter dorsal root ganglion and inhibition of subtypes of voltage-gated Ca channels. Sprague-Dawley rats with tibial nerve injury had profound and long-lasting tactile allodynia and ongoing pain. Immediate administration of R9-CBD3-A6K produced enhanced dopamine release from the nucleus accumbens shell selectively

in injured animals, consistent with relief of ongoing pain. R9-CBD3-A6K, when administered repeatedly into the central nervous system ventricles of naive rats, did not result in a positive conditioned place preference demonstrating a lack of abusive liability. Continuous subcutaneous infusion of R9-CBD3-A6K over a 24- to 72-hour period reversed tactile allodynia and ongoing pain, demonstrating a lack of tolerance over this time course. Importantly, continuous infusion of R9-CBD3-A6K did not affect motor activity, anxiety, depression, or memory and learning. Collectively, these results validate the potential therapeutic significance of targeting the CaV-CRMP2 axis for treatment of neuropathic pain.

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**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.10/D25

**Topic:** B.04. Ion Channels

**Title:** Dissecting the role of the CRMP2-Neurofibromin complex on pain behaviors

**Authors: *S. BELLAMPALLI**[1], X.-F. YANG[2], A. MOUTAL[2], Y. WANG[4], A. DORAME[3], L. A. CHEW[2], E. T. DUSTRUDE[4], B. S. SCHMUTZLER[4], M. KHANNA[2], C. M. HINGTGEN[4], T. VANDERAH[2], R. KHANNA[1]
[1]pharmacology, Univ. of Arizona, Tucson, AZ; [3]UNiversity of Arizona, [2]UNiversity of Arizona, Tucson, AZ; [4]Indiana Univ., Indianapolis, IN

**Abstract:** Neurofibromatosis type 1 (NF1) is a relatively common genetic disease primarily linked to nervous system tumors that are associated with significant chronic pain. Enhanced pain sensitivity in NF1 patients may involve the sensitization of small-diameter nociceptive sensory neurons that are known to mediate nociceptive neurotransmission. Membrane relocalization of the presynaptic N-type voltage-gated $Ca^{2+}$ channel (CaV2.2), facilitates calcitonin gene-related peptide (CGRP) release, a neurotransmitter involved in pain. CRMP2, a protein interacting with Neurofibromin, is an important mediator of CaV2.2 trafficking. Here, we examine *how* the CRMP2-neurofibromin complex controls the activity of CaV2.2. A peptide-tiling array identified a peptide within CRMP2 that bound the C-terminus of Neurofibromin: CRMP2 Neurofibromin regulating peptide 1 (t-CNRP1; where tat is the charged transduction domain from HIV-1). We tested if uncoupling the neurofibromin-CRMP2 signaling cascade could (1) affect $Ca^{2+}$ channel activity and trafficking in sensory neurons; (2) regulate evoked release of CGRP in sensory neurons from wildtype and $Nf1^{+/-}$ mice; (3) induce functional phenotypic changes in sensory

neurons; and (4) affect nociceptive function in a rodent model of neuropathic pain. t-CNRP1 inhibited $K^+$-evoked $Ca^{2+}$ influx in sensory neurons, decreased CaV2.2 membrane localization, which was related to inhibition of the CaV2.2/CRMP2/neurofibromin protein complex as evidenced by GST-pull down and proximity ligation assay (PLA). t-CNRP1 decreased the evoked release of CGRP from $Nf1^{+/-}$ mice sensory neurons. Functional fingerprinting of sensory neuron population using constellation pharmacology, showed phenotypic changes in sensory neurons treated with t-CNRP1. Finally, intrathecal administration of t-CNRP1 reversed nociceptive behavior in rodent models of inflammatory pain and post-surgical pain. These results identify t-CNRP1 as a novel tool that uncouples the CRMP2/neurofibromin and CRMP2/CaV2.2 interactions, curbs CaV2.2 activity, CGRP release and reverses nociceptive behavior. Thus highlighting the potential therapeutic significance of targeting the Neurofibromin-CRMP2-CaV2.2 axis for treatment of pain.

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**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.11/D26

**Topic:** B.04. Ion Channels

**Title:** Modulation of N-type $Ca^{2+}$ currents by agmatine in rat celiac ganglion neurons

**Authors: *Y. KIM**, S. CHUNG
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**Abstract:** Agmatine suppresses peripheral sympathetic tone by modulating Cav2.2 channels in peripheral sympathetic neurons. However, the detailed cellular signaling mechanism underlying the agmatine-induced Cav2.2 inhibition remains unclear. Therefore, in the present study, we investigated the electrophysiological mechanism for the agmatine-induced inhibition of Cav2.2 current ($I_{Cav2.2}$) in rat celiac ganglion (CG) neurons. Consistent with previous reports, agmatine inhibited $I_{Cav2.2}$ in a VI manner. The agmatine-induced inhibition of the $I_{Cav2.2}$ current was also almost completely hindered by the blockade of the imidazoline $I_2$ receptor ($IR_2$), and an $IR_2$ agonist mimicked the inhibitory effect of agmatine on $I_{Cav2.2}$, implying involvement of $IR_2$. The agmatine-induced $I_{Cav2.2}$ inhibition was significantly hampered by the blockade of G protein or phospholipase C (PLC), but not by the pretreatment with pertussis toxin. In addition, diC8-phosphatidylinositol 4,5-bisphosphate ($PIP_2$) dialysis nearly completely hampered agmatine-induced inhibition, which became irreversible when $PIP_2$ resynthesis was blocked. These results suggest that in rat peripheral sympathetic neurons, agmatine-induced $IR_2$ activation suppresses

Cav2.2 channel voltage-independently, and that the PLC-dependent $PIP_2$ hydrolysis is responsible for the agmatine-induced suppression of the Cav2.2 channel. (This study was supported by a faculty research grant fromthe Pioneer Research Center Program through the National Research Foundation of Korea funded by the Ministry of Science,ICT and Future Planning (2012-0009525)).

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**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

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**Topic:** B.04. Ion Channels

**Support:** DGAPA-UNAM

**Title:** Regulation of $Ca_V3.2$ channels by Cyclin dependent kinase 5 (Cdk5)

**Authors: *A. CALDERÓN-RIVERA**[1,2], A. SANDOVAL[3], R. GONZÁLEZ-RAMÍREZ[4], R. FELIX[1]
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**Abstract:** The $Ca_V3.2$ channel is one of the three isoforms that belongs to the Low-Voltage Activated (LVA) or T-type calcium channel subfamily. LVA channels are responsible for $Ca^{2+}$ entry at subthreshold depolarizations, regulating neuronal excitability. Hence, $Ca_V3.2$ channels are important mediators of neurotransmitter release and it is acknowledged that changes in their functional expression pattern may play a role in pathological conditions such as neuropathic pain. Recently a phosphoproteomic analysis revealed the phosphorylation map for $Ca_V3.2$ channels, however, only a few kinases have been directly involved in this posttranslational modification. Here, we report that recombinant $Ca_V3.2$ channels heterologously expressed in HEK-293 cells are regulatory targets of Cdk5. Our results indicate that coexpression of the $Ca_V3.2$ channels with the protein kinase and its activator p35 significantly upregulates $Ca^{2+}$ macroscopic currents. Site directed mutagenesis of the putative phosphorylation sites to unphosphorylatable residues showed that the relevant Cdk5 sites for $Ca_V3.2$ channel regulation centres on two amino acid residues, S561 and S1987, located in the intracellular loop connecting the II and III repeats and the C-terminal of the $Ca_V3.2\alpha1$ pore-forming subunit of the channel, respectively. These findings unveil a novel mechanism for how phosphorylation may regulate $Ca_V3.2$ channels.

**Disclosures:** **A. Calderón-Rivera:** None. **A. Sandoval:** None. **R. González-Ramírez:** None. **R. Felix:** None.

**Poster**

**467. Calcium Channel Modulation**

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**Topic:** B.04. Ion Channels

**Support:** NIH-NINDS NS029709

Blue Bird Circle Foundation

**Title:** Adrenergic signaling promotes T-type $Ca^{2+}$ channel mediated oscillatory discharges in nucleus ambiguus neurons

**Authors: *I. AIBA**, J. L. NOEBELS
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**Abstract:** Nucleus ambiguus (NA) premotor neurons contribute to the majority of parasympathetic cardiac vagal nerve fibers to reduce cardiac excitability at the SA node, where aberrant regulation can cause vasovagal syncope and cardiac arrest. Prior electrophysiological studies identified various plasticity and regulatory mechanisms of NA neurons; however most studies were conducted on neonatal preparations and might have overlooked important regulatory mechanisms present in mature brainstem. We examined the excitability of NA neurons using *in vitro* acute slice preparations obtained from young adult mice (P20-P40). Cholinergic premotor NA neurons were identified based on their expression of tdTomato fluorescence in the Chat-Cre:floxed-tdTomato mouse line. In current-clamp recordings, a brief hyperpolarizing current evoked rebound action potentials (APs) immediately following break-in, while minutes of intracellular dialysis eliminated this discharge pattern in association with a marked reduction of input resistance. Supplying spermine (0.3-0.5mM) to the intracellular solution prevented this rundown effect, suggesting that endogenous intracellular polyamines may inhibit leak currents and maintain the rebound excitation pattern. Low voltage-activated, T-type calcium current is also required for generation of the rebound discharge in NA neurons. Voltage-clamp recordings detected a significant T-current in NA neurons, and T-type current inhibitors (i.e. Z944, TTA-P2) abolished the rebound action potentials. Central adrenergic signaling is known to be involved in synaptic regulation of cardiac vagal nerve activity. We examined whether modulation of intrinsic excitability is also involved in adrenergic modulation of NA neurons. Bath application of adrenergic agonists, epinephrine (10uM) and norepinephrine (20uM), significantly increased the intrinsic excitability of NA neurons; input resistance of NA neurons was significantly increased and single evoked rebound discharges (normally composed

of 1-2 APs) converted to regenerative oscillations with >10APs and lasting up to a few seconds. T-current inhibitors again completely eliminated the adrenergic induced oscillatory activity, suggesting that T-current mediates adrenergic potentiation of intrinsic NA neuron excitability. Together this study revealed a low threshold calcium current dependent oscillatory mechanism in NA neurons and suggests that, in addition to synaptic mechanisms, modulation of intrinsic excitability may be an important site for adrenergic regulation of cardiac vagal efferent nerve activity.

**Disclosures: I. Aiba:** None. **J.L. Noebels:** None.

**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.14/D29

**Topic:** B.04. Ion Channels

**Title:** The N-type voltage-gated $Ca^{2+}$ channel is a novel substrate of the ubiquitin E3 ligase Parkin

**Authors: *L. GRIMALDO**[1], A. SANDOVAL[2], E. GARZA-LÓPEZ[3], R. FELIX[1]
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**Abstract:** N-type calcium channels ($Ca_V2.2$) are widely expressed in the brain and the peripheral nervous system, where they play important roles in the regulation of transmitter release. Although $Ca_V2.2$channel expression levels are precisely regulated, presently little is known regarding the molecules that mediate its synthesis and degradation. Previously, by using a combination of biochemical and functional analyses, we showed that the complex formed by the light chain 1 (LC1) of the microtubule-associated protein 1 B (MAP1B) and the ubiquitin-proteasome system (UPS) E2 enzyme UBE2L3, may interact with the $Ca_V2.2$ channels promoting ubiquitin-mediated degradation. The present report aims to gain insights into the possible degradation mechanisms of the neuronal $Ca_V2.2$ channel protein by the UPS. First, we identified the enzymes UBE3A and Parkin, members of the UPS E3 ubiquitin ligase family, as novel $Ca_V2.2$ channel binding partners. Immunoprecipitation assays confirmed the interaction between UBE3A and Parkin with $Ca_V2.2$ channels heterologously expressed in HEK-293 cells and in neural tissues. Parkin, but not UBE3A, overexpression led to a reduced protein level, and a decrease in the $Ca_V2.2$ channel current density. Patch clamp recordings performed in the presence of MG132 prevented the actions of Parkin suggesting enhanced channel proteasomal degradation. Together, these results indicate that Parkin mediates the proteasomal degradation of

$Ca_V2.2$. Our findings provide a novel insight into the underlying protein quality control mechanisms of $Ca_V$ channels.

**Disclosures: L. Grimaldo:** None. **A. Sandoval:** None. **E. Garza-López:** None. **R. Felix:** None.

**Poster**

**467. Calcium Channel Modulation**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 467.15/D30

**Topic:** B.04. Ion Channels

**Support:** PICT2013-1145 and PICT2015-3330 to J. Raingo

**Title:** GHSR1a constitutive activity reduces high- and low-voltage gated calcium channel surface density in a $Ca_V\beta$ dependent manner

**Authors: *E. R. MUSTAFA**[1], E. LOPEZ SOTO[2], V. MARTÍNEZ DAMONTE[1], S. RODRÍGUEZ[1], D. LIPSCOMBE[2], J. RAINGO[1]
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**Abstract:** Voltage gated calcium channels ($Ca_V$) couple plasma membrane voltage changes to calcium influx, triggering calcium-dependent processes. This sequence of fact is crucial for shaping neuronal activity. Several $Ca_V$ subtypes exist and they have different time and place specific functions in neurons. Thus, great effort has been devoted to determine what elements can control $Ca_V$ activity in neurons. In this context, many G-protein coupled receptors (GPCR) activated cascades have been detected as powerful $Ca_V$ activity modulators. On the other hand, data about the control of trafficking and density of $Ca_V$ subtypes at specific location on the neuronal plasma membrane are spare. Here we describe that a GPCR that is constitutively active (GHSR1a) in absence of its agonist (ghrelin) inhibits the forward trafficking of several $Ca_V$ subtypes. We found that the mechanism implies retention of the channel complexes at the endoplasmic reticulum and the requirement of auxiliary subunit $Ca_V\beta$. Since the solely expression of GHSR1a is enough to control $Ca_V$ trafficking and this receptor is highly expressed in brain areas controlling food intake, reward and learning and memory, our finding could have a great impact in animal behavior. Thus, further experiments focusing on the function of each $Ca_V$ subtype function are required to deeply understand the scope of GHSR1a effect on neurons.

**Disclosures: E.R. Mustafa:** None. **E. Lopez Soto:** None. **V. Martínez Damonte:** None. **S. Rodríguez:** None. **D. Lipscombe:** None. **J. Raingo:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.01/D31

**Topic:** B.04. Ion Channels

**Support:** Wellcome Trust Investigator award 098360/Z/12/Z

**Title:** Visualizing native N-type calcium channels

**Authors: *A. C. DOLPHIN**[1], K. RAMGOOLAM[2], M. NIETO-ROSTRO[2]
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**Abstract:** CaV2.2 constitutes the pore subunit of N-type calcium channels, which are important for neurotransmitter release in the central and peripheral nervous system. Immunohistochemical detection of native CaV2.2 has not been possible until now due to the low expression of these channels, and lack of suitable antibodies. We have now developed a constitutive knock-in (KI) transgenic mouse, expressing CaV2.2 with an epitope tag (2xHA) inserted in the extracellular loop between S3 and S4 of Domain II (CaV2.2_HA KI). The tag did not affect the function of the channel when expressed in vitro (Cassidy et al., 2014). In the peripheral sensory nervous system, our data show CaV2.2_HA to be expressed on the cell surface of dorsal root ganglion neurons (DRGs). In the spinal cord, CaV2.2_HA is predominantly in the superficial laminae LI and LII of the dorsal horn, mainly in the primary afferent terminals, since HA staining is reduced following rhizotomy. These mice will be instrumental in the future to understand the presynaptic role of N-type calcium channels in physiological and pathological states and will also be of use to examine the trafficking and recycling of the channels in several neural cell types. Cassidy JS, Ferron L, Kadurin I, Pratt WS, Dolphin AC (2014) Functional exofacially tagged N-type calcium channels elucidate the interaction with auxiliary alpha2delta-1 subunits. Proc Natl Acad Sci USA 111:8979-8984.

**Disclosures: A.C. Dolphin:** None. **K. Ramgoolam:** None. **M. Nieto-Rostro:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.02/D32

**Topic:** B.04. Ion Channels

**Title:** Mesoscopic cortical calcium dynamics during wakefulness, natural sleep, and anesthesia

**Authors: *L. BRIER**[1], E. C. LANDSNESS[2], P. W. WRIGHT[3], A. Q. BAUER[4], G. BAXTER[1], J.-M. LEE[2], J. P. CULVER[4]
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**Abstract:** A hallmark of non-REM sleep is the anterior to posterior propagation of slow waves (0.5-4.5 Hz) [1] and has been implicated in learning and memory consolidation. However, the cellular and molecular basis underlying slow wave oscillations remains poorly understood. Generally, slow wave sleep signals have been studied using EEG in humans, or with invasive electrophysiology in animal models. However, EEG suffers from low spatial resolution, and electrophysiology in mice is usually invasive with sparse spatial sampling. More recently, calcium indicators have been used to detect slow wave sleep using microscopy, but usually in limited fields of view. Here, we use mesoscopic calcium imaging [2] to map slow wave sleep signals throughout the cortex. Specifically, we used genetically encoded mice with a fluorescent calcium indicator (GCaMP6 driven by a Thy1 promotor in cortical neurons) to monitor the cortical calcium dynamics during anesthesia, natural sleep, and wakefulness states. Cortex was imaged transcranially through an implanted chronic optical window with the skull-intact using optical intrinsic signal (OIS) imaging. This protocol enabled consistent, repeated measurements using a CCD camera with blue light fluorescence at 17Hz while simultaneously recording EEG/EMG for state of consciousness staging and measurement of cortical global field potentials. During sleep and anesthesia there was a peak in the GCaMP power spectra over the 0.7-3 Hz range that correlated to the EEG power spectra associated with non-REM slow waves concentrated in the motor, somatosensory, and visual cortices. By combining the spatial and temporal resolution of OIS, there was an anterior to posterior propagation of the slow wave oscillations during sleep and anesthesia that disappeared during wakefulness. Functional connectivity (FC) analysis showed a transition from a binary front to back pattern in anesthesia and sleep to a more complex/local connectivity pattern seen in wakefulness. This novel imaging technique allows for high spatial and temporal resolution to study whole brain neuronal phenomenon, to study the transition between sleep and wakefulness, and has potential for applications in health and disease. References: [1] Massimini, M et al. (2004) The sleep slow oscillation as a traveling wave. *J Neuroscience* 31: 6862-6870 [2] Vanni MP, Murphy TH. (2014) Mesoscale transcranial spontaneous activity mapping in GCaMP3 transgenic mice reveals extensive reciprocal connections between areas of somatomotor cortex. *J Neuroscience* 34(48):15931-46.

**Disclosures: L. Brier:** None. **E.C. Landsness:** None. **P.W. Wright:** None. **A.Q. Bauer:** None. **G. Baxter:** None. **J. Lee:** None. **J.P. Culver:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.03/D33

**Topic:** B.04. Ion Channels

**Support:** Telethon Italy GGP14234

**Title:** Short-term plasticity of thalamocortical excitatory and inhibitory synaptic transmission in a mouse model of familial hemiplegic migraine: An excitation-inhibition imbalance revealed

**Authors: A. TOTTENE**[1], M. FAVERO[2], *D. PIETROBON[1]
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**Abstract:** Migraine is more than a headache. It is a complex brain disorder, characterized by a global dysfunction in multisensory information processing. Many migraineurs show heigthened cortical responses and impaired adaptation to repeated sensory stimulation in the period between headache attacks. The underlying cellular and network mechanisms are unknown. Given the evidence that thalamocortical (TC) networks are dysfunctional in migraine and that depression at TC synapses strongly contributes to fast adaptation of cortical responses, we studied TC synaptic transmission in a knockin mouse model of familial hemiplegic migraine type 1 (FHM1), which carry a gain-of-function mutation in the neuronal CaV2.1 calcium channel. We recorded the monosynaptic excitatory postsynaptic current (EPSC) and the disynaptic inhibitory postsynaptic current (IPSC) elicited in layer 4 (L4) regular spiking (RS) neurons of somatosensory cortex by extracellular stimulation in the ventrobasal thalamus in acute TC slices. Since the disynaptic IPSC is due to the feedforward inhibition produced by TC activation of L4 fast-spiking (FS) interneurons (INs), we also recorded the EPSC elicited by thalamic stimulation in these INs.
TC excitatory transmission on both L4 principal cells and FS INs as well as TC feedforward inhibition on RS neurons were all enhanced in FHM1 compared to WT mice. In WT mice, during repetitive thalamic stimulation at 10 Hz, short-term depression (STD) of feedforward inhibition on RS neurons and STD of the excitatory inputs on FS INs were both larger than STD of the excitatory inputs on RS neurons, resulting in a shift of the balance towards excitation during the train. In FHM1 mice, STD of the excitatory inputs on RS neurons was larger than in WT mice, as expected if the gain-of-function at TC-RS synapses is due to an increased probability of release. In contrast, STD of feedforward inhibition on RS neurons and STD of the excitatory input on FS INs were similar in WT and FHM1 mice. As a result, the shift of the balance towards excitation during repetitive thalamic stimulation was relatively smaller in FHM1 compared to WT mice.
In summary, our study shows enhanced thalamocortical synaptic transmission in a mouse model

of FHM1, and reveals a differential effect of the FHM1 mutation on short-term depression at TC synapses on L4 principal neurons and FS INs which leads to a cortical excitation-inhibition (E/I) imbalance during repetitive thalamic stimulation. These findings support the hypothesis that a reduced ability to dynamically maintain an appropriate E/I balance in different brain networks may underlie the global dysfunction in information processing typical of migraine.

**Disclosures: A. Tottene:** None. **M. Favero:** None. **D. Pietrobon:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.04/D34

**Topic:** B.04. Ion Channels

**Support:** NINDS Grant NS029709

**Title:** Development of T-type calcium channel bursting in thalamic association pathway precedes sensory pathways

**Authors: *Q. MIAO**[1], J. L. NOEBELS[1,2,3]
[1]Bayrlor Col. of Med., Dept. of Neurol., Houston, TX; [2]Dept. of Neurosci., Houston, TX; [3]Dept. of Mol. and Human Genet., Houston, TX

**Abstract:** Transient-type low-voltage activated calcium channels (T-channels) regulate the intrinsic excitability of thalamic cells and facilitate the genesis of rebound burst firing which enable thalamocortical oscillations and contribute to the modulation of brain states of awareness. The thalamus takes part in sensory, motor and cognitive functions by transmitting information to the cortex via numerous distinct nuclei. These nuclei are divided into two different categories: first order and higher order relays. First order nuclei receive driver input from the periphery or a subcortical source, while high-order nuclei mainly receive descending inputs from the cortex. Precise regulation of T channels is important for healthy thalamocortical processes since abnormal function of T-channels has been implicated in pathological conditions, including epilepsy, neuropathic pain, and sleep disorders. We examined whether different thalamic nuclei develop T-channel expression simultaneously during early development, or whether bursting in these pathways show distinctive stages of maturation? We performed whole-cell recordings in the developing mouse thalamus (postnatal day 3 to 35). We found that across subregions of the lateral thalamus, there is a high-to-low gradient from dorsal to ventral nuclei in the expression of T-channels. Specifically, all laterodorsal thalamic neurons projecting to associative retrosplenial cortex show a distinctively high expression of T-currents which enable them to fire low-threshold and rebound spikes in as early as one week old C57BL/6 mice. These spikes could be blocked by a T-channel specific blocker, Z944. At this age, a small fraction of neurons in other

higher-order nuclei including lateral posterior nucleus (LP), posterior complex (PO) and the dorsal part of medial geniculate complex (dMG) of the thalamus, can fire low-threshold and rebound spikes. In sharp contrast, similar low-threshold and rebound spikes in first-order primary sensory thalamic relay neurons, including visual (lateral geniculate nucleus, LGN), somatosensory (ventral posteromedial nucleus, VPM), and auditory (ventral part of medial geniculate complex, vMG) neurons appeared nearly one week later. This result indicates that higher-order thalamic relay neurons utilize firing supported by T-channels earlier than those in the primary sensory pathway. Although the functional development of associative cortex is poorly understood, our results reveal an early reliance on T-channels in the higher-order thalamic nuclei mediated thalamocortical pathway that might be critical for early development of limbic, spatial and cognitive processing.

**Disclosures: Q. Miao:** None. **J.L. Noebels:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.05/D35

**Topic:** B.04. Ion Channels

**Support:** CRC 1080

**Title:** Medial to lateral density gradient of T-type calcium currents in substantia nigra dopamine neurons

**Authors: *S. JAGANNATH**[1], K. M. COSTA[1,2], J. ROEPER[1]
[1]Inst. of Neurophysiol., Goethe Univ. Frankfurt, Frankfurt am Main, Germany; [2]Intl. Max Planck Res. Sch. for Neural Circuits, Max Planck Inst. for Brain Res., Frankfurt am Main, Germany

**Abstract:** The substantia nigra (SN) dopamine (DA) neurons possess an intrinsic pacemaker mechanism that engages a variety of voltage-gated calcium channels (VGCCs). However, the functional contributions of distinct VGCCs are not well understood. Also, it is unclear whether VGCCs have uniform roles across the medial to lateral extent of the substantia nigra. Therefore, we investigated the densities and functional roles of VGCCs for pacemaker frequency and precision control across the entire SN using acute midbrain slices of adult (3-4month old) male C57BL/6N mice. For immunohistochemical and morphological identification all neurons were filled with neurobiotin and processed for TH-immunohistochemistry. Whole-cell patch-clamp experiments demonstrated that the density of low-voltage activated (LVA) calcium currents increased about 2-fold with a medial to lateral gradient across the SN (linear regression, slope = 20 pA/pF per 100µm, $r^2 = 0.12$, $p < 0.0001$; n = 132). In contrast, high-voltage activated (HVA) calcium current densities did not systematically vary with their medial to lateral positions ($r^2 <$

0.001, p = 0.732; n = 132). In addition, peak LVA calcium current amplitudes were reached at significantly more negative membrane potentials in lateral SN compared to medial DA SN neurons, while no differences in voltage dependence were observed for HVA peak currents. These results indicated a topographically organized diversity of LVA calcium channels for DA SN neurons along the medio-lateral axis. To study the functional implications of the LVA calcium channel gradient, we carried out cell-attached patch-clamp recordings to record changes of spontaneous pacemaker activity in response to the LVA ($Ca_v3$) calcium channel blocker nickel. In accordance with the differences in LVA calcium channels densities, bath application of 100 µM nickel decreased pacemaker precision (quantified as coefficient of variation, CV) to a greater extent in lateral compared to medial DA SN neurons (CV, lateral control: 12.2 ± 0.87 %, + 100 µM nickel: 17.2 ± 1.7 %, n = 17; p = 0.004; medial control: 12.1 ± 2.65 %, + 100 µM nickel: 15.1 ± 2.43 %, n = 13; p = 0.01). Taken together, these findings demonstrate that medial to lateral gradients of ion channel expression in DA SN neurons in the substantia nigra are associated with functional differences in pacemaker control.

**Disclosures: S. Jagannath:** None. **K.M. Costa:** None. **J. Roeper:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.06/D36

**Topic:** B.04. Ion Channels

**Support:** NIH Grant AG047744-03

**Title:** “Leaky” ryanodine receptors: Potential role in age-related cognitive decline and the pathogenesis of Alzheimer’s disease

**Authors: *D. DATTA**, A. F. T. ARNSTEN, C. D. PASPALAS
Yale Univ., New Haven, CT

**Abstract:** The newly evolved prefrontal cortex (PFC) mediates highest-order cognition, and is markedly afflicted in age-related cognitive disorders such as Alzheimer’s disease (AD). Within the PFC, modules of pyramidal cells in layer III microcircuits engage in recurrent excitation to sustain persistent neural firing required to maintain working memory, a prototypic cognitive function mediated by the PFC. With advancing age, rhesus monkeys show atrophy of dendritic spines in layer III, evidence of disinhibited cAMP-PKA-calcium signaling and a rise in phosphorylated tau. Ryanodine receptors (RyRs) mediate internal calcium release from the sarcoplasmic and smooth endoplasmic reticulum (SER), in myocytes and neurons, respectively. In aged cardiac muscle, elevated cAMP-PKA-calcium signaling due to age-related loss of the cAMP-specific phosphodiesterase, PDE4D, phosphorylates RyR2 (pRyR2), and increases

calcium conductance inducing calcium “leak”. We hypothesize that a similar sequence occurs in aging PFC due to its unique molecular regulation by cAMP, leading to cognitive deficits. Using high-resolution immunoelectron microscopy, we studied the localization and spatial interactions of pRyR2 and PDE4D in young vs. aged monkey and rodent PFC. Preliminary work shows pRyR2-reactive SER membranes in dendritic spines. A parallel study tested whether acute treatment with S107, a novel compound that stabilizes the interaction between pRyR2 and downstream signaling protein calstabin2 to prevent calcium leak in cardiac muscle, improved cognitive function in aging monkeys and rats. Our behavioral analysis using the delayed alternation task in aged rats suggests significant enhancement of spatial working memory following low doses of S107. S107 has already been shown to rescue cardiac deficits and protect from stress-induced hippocampal memory function, encouraging the success of this approach. This research may provide a novel therapeutic strategy for early protection of the higher brain circuits most vulnerable to degeneration. Together, these studies elucidate how molecular changes with age initiate the degenerative process in the PFC and reinforce the idea that dysregulated calcium signaling is a key event in susceptible cortical microcircuits, supporting early theories of AD etiology.

**Disclosures:** **D. Datta:** None. **A.F.T. Arnsten:** None. **C.D. Paspalas:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.07/D37

**Topic:** B.04. Ion Channels

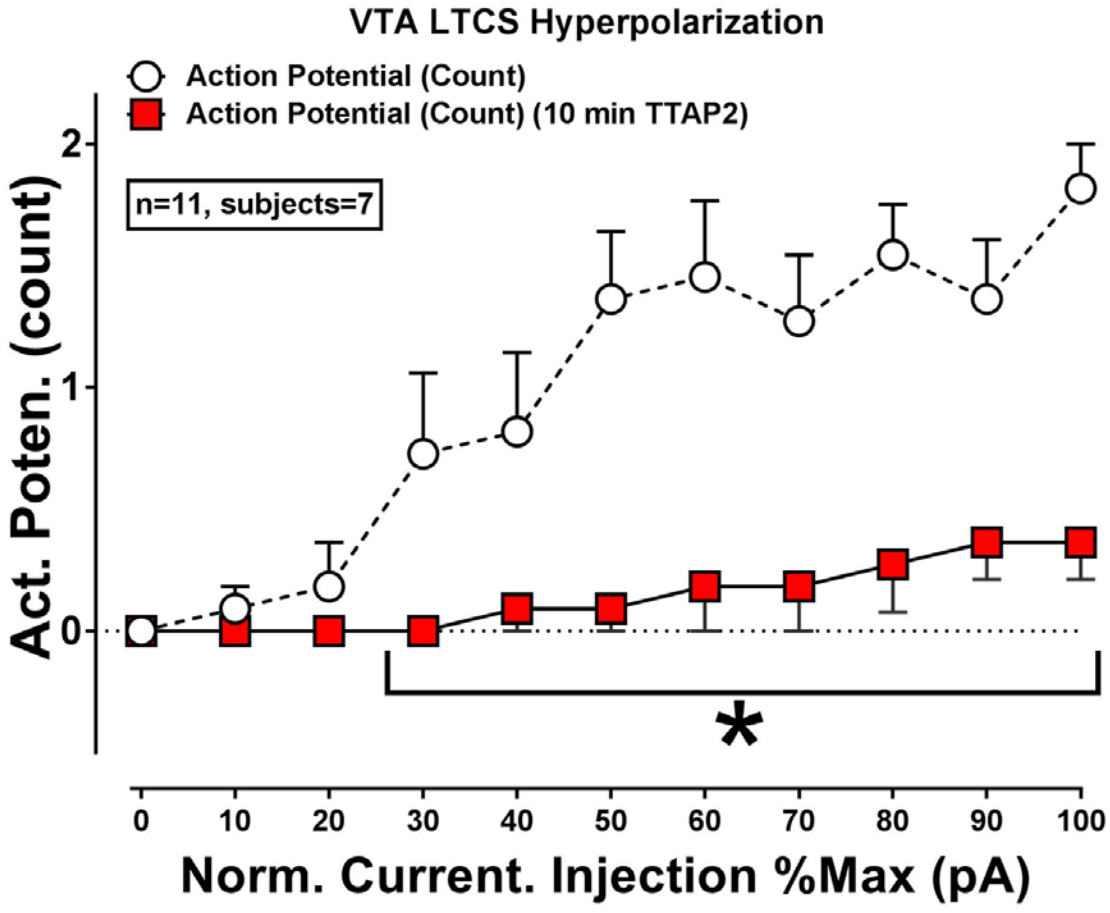
**Support:** NIH Grant GM102525

**Title:** T-type calcium channels contribute to neuronal excitability within the ventral tegmental area

**Authors: *M. E. TRACY**, S. TODOROVIC
Anesthesiol., Univ. of Colorado-Denver, Aurora, CO

**Abstract:** *Rationale* There is an emerging body of evidence that implicates a role of voltage gated calcium channels in contributing to the excitability of neurons within the mesolimbic reward system. While most research attention has centered on high voltage L-type calcium channel activity, the presence and role of the low voltage-gated T-type calcium channel has not been well explored. Therefore T-type calcium channel activity may represent an unexplored system that contributes to neuronal excitability within the ventral tegmental area (VTA). *Objectives* We tested the hypothesis that the CaV 3.1 T-type calcium channel plays an integral role in neuronal excitability in both dopaminergic and non-dopaminergic neurons of the ventral

tegmental area utilizing wild-type (WT) rats and mice, TH-eGFP knock-in rats and CaV 3.1 knock-out mice in acute horizontal brain slices of adolescent subjects.
*Results* In voltage clamp, we assessed first T-type channel activity with steady-state inactivation curves in both WT rats and mice and found similar mid-point of inactivation (V50) of -94.35 and -90.51 mV, respectively. Application of the selective pan-T-type channel antagonist TTA-P2 at 5 uM ablated these currents in both rats and mice. Furthermore, in CaV 3.1 knockout mice no currents were observed that matched the electrophysiological properties of T-type channels. In ensuing current-clamp experiments, we observed the presence of hyperpolarization-induced rebound action potentials in a subset of dopaminergic and non-dopaminergic neurons within the rat VTA. Following the application of 5 µM TTAP2, rebound action potentials were significantly inhibited ($p<0.01$).
*Conclusions* These results demonstrate for the first time that in a subset of neurons within the VTA, T-type CaV3.1 channels play a functional role in inducing repeated action potentials following brief periods of hyperpolarization. Given the complex role between inhibitory interneurons and dopaminergic neurons in the VTA in mediating temporally discrete motivated behaviors, these results suggest a substantial role for T-type channels.




**Disclosures:** **M.E. Tracy:** None. **S. Todorovic:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.08/D38

**Topic:** B.04. Ion Channels

**Support:** NIH Grant GM-102525

**Title:** Cav3.1 channels are important for isoflurane inhibition of neuronal excitability in the central medial thalamic nucleus

**Authors: *T. TIMIC STAMENIC**, S. TODOROVIC
Anesthesiol., Univ. of Colorado Denver, Anschutz Med. Ca, Aurora, CO

**Abstract:** Thalamocortical circuits are important for the regulation of arousal and central medial nucleus (CeM) as a part of intralaminar thalamus acts as a key hub through which general anesthesia is initiated. It is well known that low-voltage-activated T-type calcium channels (T-channels) are abundantly expressed in the thalamus where they regulate neuronal excitability but their role in CeM during anesthesia was not examined. Here, we investigated properties of T-type calcium channels and effect of isoflurane in CeM using patch-clamp technique in acute coronal brain slices of adolescent wild type C57BL/6J (WT), 3.1 knock-out (KO) and 3.2 KO mice. Voltage-clamp recordings showed that there is a large depolarizing shift in steady-state activation curves of about 20 mV in 3.1 KO mice when compared with WT and 3.2 KO mice ($p<0.001$). Smaller but significant shift of about 4 mV was achieved in steady-state inactivation kinetics between 3.1 KO and 3.2 KO mice. Current density was also decreased by about 90% in 3.1 KO mice in comparison to WT and 3.2 KO mice ($p<0.001$). Additionally, 3.2 KO mice had a smaller decrease in current density of about 10% in comparison to WT mice ($p<0.05$). Isoflurane at clinically-relevant concentrations decreased T-current density by about 40% ($p<0.001$) and induced hyperpolarizing shift of 8 mV in WT mice in steady-state inactivation curves. Moreover, isoflurane reduced time constant of macroscopic current inactivation kinetics (tau). Current-clamp recordings revealed that there are no significant differences in tonic action potential frequency between WT, 3.1 KO and 3.2 KO mice. The statistically significant reduction in low-threshold spike (LTS) amplitude was in 3.2 KO in comparison to WT mice ($p<0.01$), while in 3.1 KO mice rebound burst with LTS was completely abolished. Finally, we used current-clamp recordings to investigate the effects of isoflurane on firing patterns and passive membrane properties of CeM neurons in WT and 3.1 KO mice. We found that isoflurane reduced tonic action potential frequency by 35% over the wide range (50—200 pA) of current injections ($p<0.001$), decreased LTS amplitude by 55% ($p<0.001$), while slightly increased input resistance by 15% ($p<0.001$) in WT mice. On contrary, isoflurane decreased tonic action potential frequency in Cav3.1 KO mice only during maximal current injections of 200 pA ($p<0.01$). We

conclude that 3.1 T-channels are dominant isoform in the CeM and that there is a profound sensitivity of these T-channels to isoflurane. These findings reveal a crucial role of T-channels in CeM in arousal suppression during isoflurane anesthesia.

**Disclosures: T. Timic Stamenic:** None. **S. Todorovic:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.09/D39

**Topic:** B.04. Ion Channels

**Support:** 2 T32 MH 19524-24

**Title:** Exaggerated homeostatic adaptation to inactivity in Timothy Syndrome

**Authors: *S. D. SUN**[1,2], B. S. SUUTARI[1], N. MANDELBERG[2], B. LI[2], N. CHENOUARD[2], R. W. TSIEN[2]
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]Neurosci. Inst., NYU Langone Med. Ctr., New York, NY

**Abstract:** Homeostasis is form of neuronal plasticity that serves to maintain neuronal and network stability and works to oppose destabilizing Hebbian plasticity. Dysfunctional homeostatic plasticity has been suggested as a possible pathogenic mechanism underlying Autism Spectrum Disorders (ASD). To investigate this hypothesis, we studied multiple mechanisms of homeostatic adaptation in a mouse model (TS2-neo) of Timothy Syndrome (TiS). TiS is a syndromic form ASD that arises from a mutation in the pore-forming subunit of the $Ca_V1.2$ calcium channel (CaCh). TS2-neo animals display ASD behaviors and increased interictal activity, providing a validated animal model to study alterations in neuronal functioning both *in vitro* and *in vivo*. Our studies reveal intriguing differences in the homeostasis of synaptic weights and intrinsic excitability in TiS cortical pyramidal neurons. We have conducted a series of *in vitro* experiments to assess changes in the homeostatic plasticity of unitary neurotransmission and spike firing, using dissociated cultures from cortices of heterozygous TS2 and wild type (WT) siblings. We measured miniature postsynaptic currents (mEPSCs) of pyramidal neurons of TS2 and WT cultures between 13-16 days *in vitro* (DIV) and found that after 24h of action potential (AP) blockade by chronic tetrodotoxin (TTX) treatment, mEPSC amplitudes increased in both TS2 and WT pyramidal neurons. TS2-neo pyramidal neurons exhibited an exaggerated upregulation in amplitude and frequency. This was accompanied by higher intensity of GluA1-containing AMPA receptors at synapses in TS2 pyramidal neurons when compared to WT after TTX. In parallel, we observed a similarly exaggerated homeostatic adaptation of intrinsic excitability in TS2 neurons. Without chronic

TTX treatment, both WT and TS2 pyramidal neurons fired at similar frequencies in response to increasing current injections. These response frequencies increased after TTX treatment in both WT and TS2, with TS2 neurons firing spikes at higher frequencies and with longer half-widths than WT. Using electrophysiology and calcium imaging, we have identified differences in the spontaneous firing patterns of TS2 neurons and networks (compared to WT) only after engaging in homeostasis. Lastly, we have observed similar electrophysiological alterations in layer 2/3 pyramidal neurons in primary visual cortex recorded *ex vivo* from visually deprived WT and TS2 animals. These results suggest that $Ca_V1.2$ has a key role reporting levels of activity to numerous mechanisms of homeostatic autoregulation and encourage further exploration into the contribution of these dysfunctional mechanisms to ASD.

**Disclosures: S.D. Sun:** None. **B.S. Suutari:** None. **N. Mandelberg:** None. **B. Li:** None. **N. Chenouard:** None. **R.W. Tsien:** None.

**Poster**

**468. Calcium Channels**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 468.10/D40

**Topic:** B.04. Ion Channels

**Support:** Fondazione Telethon (grant # GGP15110)

**Title:** Attenuated L-type $Ca^{2+}$ currents, inactivation gating and action potential firing in adrenal chromaffin cells of a Timothy syndrome mouse model (TS2-neo) with autistic traits

**Authors: *E. CARBONE**[1], C. CALORIO[1], L. GUARINA[1], D. GAVELLO[1], A. MARCANTONI[1], P. DEFILIPPI[1], F. BALZAC[1], E. TURCO[1], G. C. L. BETT[2], R. L. RASMUSSON[2]
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**Abstract:** Timothy syndrome (TS) is a rare genetic disease caused by a single point mutation (G406R) in the pore forming α1-subunit of L-type Cav1.2 calcium channels (CACNA1C) that generates long-QT and autism spectrum disorder. TS exists in two forms: a milder (TS1) and a more severe (TS2) that arise from the same missense mutation (G406R) in the alternatively spliced exons (8A and 8) that code for the IS6 transmembrane segment of Cav1.2 channels (Splawski et al, 2004; 2005). TS2 is associated to the G406R mutation of exon 8 that is highly expressed in human brain and heart (Splawski et al, 2005) and causes marked decrease of Cav1.2 channel inactivation with consequent increased $Ca^{2+}$-entry into the cell.
Recently, Bader et al (2011) generated a TS2-like mouse with the G406R mutation in exon 8. Heterozygous and homozygous TS2 mice have low rate of survival. However, heterozygous

mice that are allowed to keep an inverted neo-cassette in exon 8A (TS2-neo) survive well to adulthood and are shown to recapitulate triad of autistic traits. Taking advantage of this mouse model and that Cav1.2 exon 8 is highly expressed in human adrenal glands (Splawsky et al, 2005), we studied the functional changes that the TS2 mutation induces to the $Ca^{2+}$ currents and action potential (AP) firing of adrenal chromaffin cells. Mouse chromaffin cells (MCCs) possess high densities of Cav1.2 and Cav1.3 channels (50% of total) and is thus a good cell model to test how the blunted expression of mutated Cav1.2 channels alter $Ca^{2+}$ currents and cell excitability. Here we show that $Ca^{2+}$ currents (N, P/Q, R and L-type) of MCCs of TS2-neo mice are strongly reduced with respect to WT. Peak $Ca^{2+}$ current is 84 vs 142 pA at +20 mV in 10 mM $Ca^{2+}$. The same 40% reduction is evident on the L-type currents obtained by subtracting DHP-insensitive currents (recorded in 5 μM nifedipine) from control, suggesting unspecific Cav channels down-regulation in mutated MCCs. TS2-neo L-type currents activate at about the same potential of WT currents ($V_{1/2}$ -19 vs -18 mV) but are significantly less inactivating as demonstrated by the 40% reduced rate of fast inactivation and the 45% attenuated "U-shaped" curve of $Ca^{2+}$-dependent inactivation. TS2-neo MCCs exhibit more negative resting potentials than WT (-54 vs -48 mV), which cause a reduced percentage of spontaneously firing MCCs (10 vs 70%). Evoked APs in mutated MCCs have unchanged rheobase (2-3 pA) but are typically undershoot. In conclusion, the TS-2 mutation causes a drastic decrease of functional Cav and Nav channels that support AP firing in MCCs. This may derive from the increased $Ca^{2+}$ leak into the cell at rest induced by the less inactivating Cav1.2 channels that are already available at $V_{rest}$.

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**Poster**

**468. Calcium Channels**

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**Title:** Local $Ca_V1$ L-type calcium channel activity synergistically signals to the nucleus

**Authors: *N. MANDELBERG**[1], B. LI[2], R. W. TSIEN[2]
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**Abstract:** Excitation-transcription (E-T) coupling, the process by which electrical changes across a cell's membrane regulate transcription, is critical in neurons for many physiological processes. Intracellular calcium is an essential messenger in this process, making sources of neuronal calcium and their connections to the nucleus of great interest. L-type calcium ($Ca_V1$) channels dominate the control of gene expression from the dendrite, as calcium influx mobilizes a signaling cascade relying on the action of a group of calcium/calmodulin (CaM)-dependent kinsases (CaMKs) to activate the nuclear transcription factor calcium- and cAMP-response element binding protein (CREB). The constituents of this pathway are implicated not only in neuropsychiatric disease, but also in several processes essential for normal neuronal function. We have recently shown that $Ca_V1$ channels can signal through voltage-dependence conformational changes (VDC), which are able to synergize with the activity of other calcium-permeable channels. To determine how these interactions could contribute to neuronal E-T coupling, we pharmacologically isolated $Ca_V1$ VDC and ionic flux from *N*-methyl-D-aspartate (NMDA) receptors. Here we provide evidence that NMDA receptor stimulation requires $Ca_V1$ VDC to activate neuronal CREB. Furthermore, we use different calcium chelators and co-immunoprecipitation to show that this functional relationship between $Ca_V1$ and NMDA receptors is based on close spatial and structural relationships. Finally, we show that these channels contribute to CREB activation by quantal events in the absence of whole-cell spikes, suggesting that localized stimuli are capable of mobilizing these pathways to reach the nucleus. Together, these results suggest that $Ca_V1$ channels can exert control over neuronal transcription based on local signals that interact not only with downstream signaling partners, but other channels at the dendritic spine as well.

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**Poster**

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**Title:** Alterations of the $Ca_v1.4$ C-terminal automodulatory domain unmasks an atypical form of calmodulin regulation on $Ca^{2+}$-dependent inactivation and activation

**Authors: *B. WILLIAMS**[1,2], A. LEE[2]
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**Abstract:** To support its role in mediating tonic exocytosis at the photoreceptor synapse, $Ca_v1.4$ L-type $Ca^{2+}$ channels undergo weak $Ca^{2+}$-dependent inactivation (CDI). The mechanism involves a C-terminal automodulatory domain (CTM) that competes with calmodulin (CaM) binding to the channel. A mutation that causes congenital stationary night blindness (CSNB2), K1591X, causes premature truncation of the channel just downstream of the CaM binding region and removal of the entire CTM. The mutant channels ($Ca_v1.4$K1591X) exhibit strong CDI and activation at more negative voltages than full-length channels similar to a splice variant ($Ca_v1.4\Delta$ex47) that lacks just a portion of the CTM. To determine if selective deletion of exon 47 causes distinct regulation of CDI and activation as compared to the K1591X mutation, we compared the properties of $Ca_v1.4$K1591X and $Ca_v1.4\Delta$ex47 in electrophysiological recordings of transfected HEK293T cells. We found key differences in how CaM regulates CDI of these channels. First, $Ca_v1.4$K1591X undergoes significantly faster CDI than $Ca_v1.4\Delta$ex47. Second, CDI of $Ca_v1.4\Delta$ex47 can be suppressed by dominant negative expression of CaM mutants that cannot bind $Ca^{2+}$ in either the C-terminal ($CaM_{34}$) or N-terminal ($CaM_{12}$) lobe, whereas only $CaM_{34}$ blunts CDI of $Ca_v1.4$K1591X. Third, $CaM_{12}$ reverses the negative shift in activation of $Ca_v1.4\Delta$ex47 but not of $Ca_v1.4$K1591X. We conclude that the deletion of exon 47 alters how CaM functionally interacts with the channel in a way that is not reproduced by the K1591X mutation, which may contribute to the pathological effects of K1591X for $Ca^{2+}$ signaling at the photoreceptor synapse.

**Disclosures: B. Williams:** None. **A. Lee:** None.

**Poster**

**468. Calcium Channels**

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**Support:** ITN Switchboard 674901 to AK and ES, FWF P26881 to AK, University of Innsbruck and Center for Molecular Biosciences Innsbruck

**Title:** Rewiring of bipolar cells in a mouse model of congenital stationary night blindness type 2

**Authors: *I. KILICARSLAN**[1], H. SEITTER[1], E. STRETTOI[2], A. KOSCHAK[1]
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**Abstract:** Human mutations in the CACNA1F gene - encoding Cav1.4 L-type calcium channels - are associated with congenital stationary night blindness type 2 (CSNB2). In the retina Cav1.4 channels are predominantly expressed at photoreceptor (PR) terminals and most likely also in bipolar cells (BC) where they allow sustained calcium influx and ensure neurotransmitter release. Due to their important role for PR synapse formation and maturation we compared two Cav1.4 mouse models (Cav1.4-KO, loss-of-function; Cav1.4-IT, gain-of-function) with respect to differential effects on retinal morphology. Both mouse models showed structural remodeling of rod BCs obvious from their elongated dendrites, the disrupted organization of the outer plexiform layer and immature PR synaptic ribbons. However, structural aberrations seemed more pronounced in Cav1.4-KO retinas. Immunohistochemical stainings using anti-PSD95 showed that in Cav1.4-IT PR terminals were mislocated in the ONL and contained mostly elongated ribbons as seen in co-stainings with the ribbon marker CtBP-E12 (*N = 4 for WT, Cav1.4-IT and Cav1.4-KO*). Co-staining with PKCα showed that in some displaced terminals contacts with rod BCs are still formed whereas in others invaginating contacts are absent. The latter suggested that those rod BCs however try to form new connections in the ONL. Cav1.4-KO mice ribbons showed only circular appearance and PSD95 protein was undetectable (*N = 3 for WT and Cav1.4-KO*). Preliminary analyses implicated that in retinas of older (28 weeks) Cav1.4-IT animals rod BC dendrites were completely lacking in the peripheral part of the retina, likely due to the absence of photoreceptors in the corresponding area. Using secretagogin as a marker for cone BCs in Cav1.4-IT animals we detected also sprouting cone BCs in 4 animals indicating that bipolar cells in the cone pathway are also affected. Our data support a crucial role of Cav1.4 channels for proper formation of photoreceptor to bipolar cell contacts. Moreover, we suggest that different Cav1.4 mutations can cause different types of morphological aberrations likely to affect also the functional outcome. Such differences may also explain subtle variations in the clinical manifestation of CSNB2.

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**Title:** Light induced ganglion cell responses in Cav1.4 mutant mouse retinas

**Authors: *L. ZANETTI**, H. SEITTER, A. KOSCHAK
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**Abstract:** Mutations in the CACNA1F gene encoding for the alpha1 subunit of Cav1.4 channels are known to cause Congenital Stationary Night Blindness Type 2 (CSNB2). Typical symptoms in CSNB2 are moderately low visual acuity, myopia, nystagmus and variable levels of night blindness or progressive photophobia. The Cav1.4 I745T (IT) mutation is associated with this disease and in heterologous expression system, has been shown to result in gain of Cav1.4 channel function. How such abnormal calcium influx can affect the retinal circuits is hardly known. Our previous work has demonstrated that the IT mutation caused disturbances in the signal transmission of mouse retinas using multielectrode array recordings upon visual stimulation in mesopic conditions. The aim of the current study is to further examine the ganglion cell (GC) activity of IT mouse retinas under both dim light (scotopic) and bright light (photopic) conditions, and by the means of multiple light stimuli aimed to detect specific GC response patterns. We confirmed a higher spontaneous firing rate in the absence of stimuli and a delayed response in both light conditions in IT whole-mount retinal preparations. In addition, compared to controls, IT retinas showed a diminished firing frequency within the stimulus (WT= 16 Hz, IT= 6.7 Hz, mean of 5 and 4 experiments respectively). The higher spontaneous firing rate and the decreased light-driven firing response likely account for the inability of GC to transduce efficiently visual signals. Of note many GC previously did not respond to full-field stimulation under mesopic light conditions. In this study, the analysis of the same cell in two different light conditions showed that ON and OFF responses of IT GC are largely lost during bright light: while 275 GCs responded to dim light, only 80 GC (N= 4) responded using bright light stimuli. Gaussian white noise stimulus analysis instead, showed a loss of GCs response also at scotopic level. These preliminary data indicate that, although scotopic and photopic pathways show similarly impaired responses, in the IT CSNB2 model the cone pathway might be more severely affected. Together our findings reflect what is seen in electroretinographic analyses of CSNB2 patients.

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**Poster**

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**Title:** $\alpha_2\delta$-4 is required for maintaining the molecular and structural organization of rod and cone photoreceptor synapses

**Authors: *A. LEE**[1], V. KEROV[1], J. LAIRD[2], M.-L. JOINER[1], D. SOH[1], J. HAGEN[1], S. GARDNER[2], B. WILLIAMS[1], T. YOSHIMATSU[4], S. BHATTARAI[3], T. PUTHUSSERY[5], N. ARTEMYEV[1], A. DRACK[3], R. O. WONG[4], S. BAKER[2]
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**Abstract:** $\alpha_2\delta$-4 is an auxiliary subunit of voltage-gated $Ca_v1.4$ L-type channels that are required for the development and mature exocytotic function of the photoreceptor ribbon synapse. Although human mutations in the CACNA2D4 gene encoding $\alpha_2\delta$-4 cause heterogeneous visual phenotypes and defects in synaptic transmission primarily by cone photoreceptors, abnormalities in rod but not cone synapses have been reported previously in $\alpha_2\delta$-4-deficient mice. Here, we describe a new knock-out ($\alpha_2\delta$-4 KO) mouse model in which both rod and cone synapses are disrupted but in different ways. In $\alpha_2\delta$-4 KO mice, ribbons and key synaptic proteins are lost to a greater extent from terminals of rods than cones, and ectopic ribbons and processes of horizontal cells and bipolar cells extend abnormally into the outer nuclear layer. $Ca_v1.4$ channels are progressively lost first in rods and later in cones of $\alpha_2\delta$-4 KO mice. Serial electron microscopy revealed an absence of invaginating horizontal and bipolar processes into $\alpha_2\delta$-4 KO cone pedicles, despite the presence of morphologically normal ribbons. Rod and cone synaptic transmission is nearly undetectable in electroretinograms of $\alpha_2\delta$-4 KO mice, despite the partial preservation of both rod- and cone-mediated vision in a behavioral assay. We conclude that $\alpha_2\delta$-4 plays an essential yet distinct role in maintaining the structural and functional integrity of rod and cone synapses, the disruption of which may contribute to visual impairment in humans with CACNA2D4 mutations.

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**Poster**

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**Title:** Mechanisms of modulating dendritic spine morphology by $Ca_V1.3$ L-type calcium channels

**Authors: *R. I. STANIKA**[1], J. STRIESSNIG[2], M. CAMPIGLIO[1], G. J. OBERMAIR[1]
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**Abstract:** L-type $Ca^{2+}$ channels (LTCC) regulate activity-dependent neuronal development, synaptic plasticity, and gene transcription and altered channel activity has been associated with aberrant brain function and neurological disease. Recently we demonstrated that the LTCC $Ca_V1.3$ modulates postsynaptic dendritic spine stability, thereby providing a potential mechanism linking channel function to pathological alterations. Expression of short $Ca_V1.3$ splice variants ($Ca_V1.3_{42A}$, $Ca_V1.3_{43S}$) or deletion of the C-terminal PDZ-binding sequence in the full-length $Ca_V1.3_L$ induced aberrant dendritic spine elongation, whereas expression of the full-length channel alone stabilized dendritic spines. The observed morphological changes correlated with increased somatic $Ca_V1.3$ currents and dendritic calcium signals suggesting a major role of the dendritic calcium load in the regulation of postsynaptic stability. Alternatively, signaling via the C-terminal PDZ-protein interactions may be involved in the structural synaptic remodeling. In order to provide novel insights into the underlying mechanisms, here we studied dendritic spine modulation by $Ca_V1.3$ channels in hippocampal cultures from $Ca_V1.3$ knockout mice and analyzed the consequences on postsynaptic AMPA receptor distribution and CaMKII autophosphorylation. Hippocampal neurons lacking $Ca_V1.3$ calcium channels showed normal dendritic development and dendritic spine formation. Reconstituting the neurons with full-length $Ca_V1.3_L$ resulted in a slightly increased spine density and a larger fraction of mature mushroom-like spine. Consistent with our previous findings the expression of a $Ca_V1.3$ channel with a deleted C-terminal PDZ-binding sequence ($Ca_V1.3_{\Delta ITTL}$) significantly increased spine size and induced the formation of more filopodia-like spines. These changes were accompanied by a redistribution of surface AMPA receptors from dendritic spines to shafts. Preliminary data indicated associated changes in the level of T286 autophosphorylated CaMKII thereby providing a link between $Ca_V1.3$ channel activity and F-actin-mediated dendritic spine remodeling. Taken together, our data suggest that calcium influx through $Ca_V1.3$ channels regulates dendritic

spine morphology via CaMKII/F-actin signaling and affects postsynaptic AMPA-receptor abundance.

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**Poster**

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**Title:** Tissue-specific and developmental expression of Cav1.3 splice isoforms in the I-II linker

**Authors:** ***B. LACARUBBA**[1], A. BUNDA[2], K. SAVAGE[3], T. FOXALL[3], A. S. ANDRADE[4]
[1]Biol. Sci., Univ. of New Hampshire, Durham, NH; [2]Univ. of New Hampshire, DURHAM, NH; [4]Dept. of Biol. Sci., [3]Univ. of New Hampshire, Durham, NH

**Abstract:** $Ca_V1.3$, an L-type voltage-gated calcium channel, is highly expressed in neurons and neuroendocrine cells. $Ca_V1.3$ is involved in several functions including neurotransmitter release, peptide release, pace-making activity and gene expression. The *CACNA1D* gene, the pore-forming subunit of $Ca_V1.3$, is linked to several neurological, gland and heart-related disorders including autism, primary aldosteronism and sinoatrial node dysfunction and deafness syndrome respectively. This suggests tissue-specific roles. Alternative splicing of the *CACNA1D* ($Ca_V1.3$) pre-mRNA is critical in generating molecular and functional diversity of $Ca_V1.3$. The cassette exon (e11) encodes for 20 amino acids within the I-II linker, and generates two isoforms e11 and Δ11. This region of the channel is important for membrane targeting, and coupling to signaling cascades, which opens the possibility that e11 affects cell-specific functions of $Ca_V1.3$. Genotype-tissue expression data from the GTEx portal suggests that $Ca_V1.3$ generates tissue-specific splice isoforms. Here we further characterized the tissue expression of e11 and Δ11 in a series of RNA samples derived from human tissues. In adult tissues, we found the highest levels of e11 expression relative to Δ11 in cortex (88 ± 1.2%), cerebellum (87 ± 0.4%) and hippocampus (82 ± 1.3 %), whereas less levels of expression are seen in spinal cord (44 ± 2.6%). Global knock out of the splicing factors Mbnl1, Mbnl2 and Rbfox1 show reduced expression of e11. These splicing factors are key for developmental regulation of alternative splicing, and suggest that e11 is also regulated during development. To test for this we quantified expression levels for e11 and Δ11 in RNA from fetal and adult human samples, and we found a striking switch from Δ11 to e11 (0% to 100%). We also performed a developmental curve in mouse whole brain tissue, and we found a similar pattern of expression relative to human tissues. Δ11

isoform dominates early in development, whereas the e11 isoform dominates later in development. This switch occurs during the critical period in mice (9-30 days). Our results show that e11 is tissue-specific and heavily regulated during development. Further studies will be performed to understand the functional relevance of this exon in native systems.

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**Poster**

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**Support:** R00-MH099405

**Title:** Alternative splicing of $Ca_V2.2$ pre-mRNA influences cued fear conditioning in a sex-dependent manner

**Authors: *A. BUNDA**, B. LACARUBBA, A. ANDRADE
Univ. of New Hampshire, Durham, NH

**Abstract:** Presynaptic N-type ($Ca_V2.2$) voltage-gated calcium channels control transmitter release in various areas of the nervous system. Alternative splicing of the cassette exon 18a (e18a) on the cytoplasmic II-III linker of $Ca_V2.2$ generates two splice isoforms (+18a and Δ18a) with unique biophysical properties. 18a splice isoforms are more resistant to inactivation during repetitive stimulation, and produce larger calcium currents than Δ18a isoforms in both mammalian expression and native systems. Δ18a isoform is dominant over +18a (~87% vs ~13%) in medial prefrontal cortex (PFC), ventral hippocampus and amygdala. All these areas are involved in fear-related behavior. To assess the behavioral role of the cassette exon 18a in these brain areas, a mouse line was generated that globally expresses only the +18a isoform of $Ca_V2.2$ (18a-only), thus eliminating the ability of the system to exclude e18a. We performed several assays in both the 18a-only and wild-type (WT) mouse lines for both sexes, including contextual and cued fear conditioning to assess hippocampus and amygdala respectively, and cued fear extinction and retention to assess cortical areas. We found that 18a-only females show enhanced freezing to the cue during the initial five tones of fear extinction retention relative to WT (18a-only = 45.4 ± 8s, WT = 23.2 ± 6s, $p = 0.037$), indicating a potential e18a-dependent difference in cortical function. No differences were observed for females during fear acquisition, contextual fear conditioning or cued fear extinction. By contrast, males of both genotypes showed similar fear responses for all protocols. Our preliminary results suggest the repression of cassette exon 18a in $Ca_V2.2$ is important for retention of cued fear extinction in female mice. This may involve

PFC, but not amygdala or hippocampal areas. Given that e18a expression may influence the PFC, this area will be the target for future studies.

**Disclosures:** **A. Bunda:** None. **B. LaCarubba:** None. **A. Andrade:** None.

**Poster**

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**Title:** Regulation of astrocyte calcium signaling and gliotransmission by store-operated CRAC channels

**Authors: *A. B. TOTH**, K. HORI, M. PRAKRIYA
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**Abstract:** Astrocytes comprise the major cell type in the central nervous system (CNS) and regulate numerous functions including CNS development, homeostasis, and repair. Recent evidence indicates that astrocytes also play a direct role in modulating synaptic transmission by secreting 'gliotransmitters' such as glutamate and ATP. To support their role in synaptic physiology, astrocytes are intimately associated with pre- and post-synaptic neuronal membranes in an anatomical unit known as the tripartite synapse, allowing astrocytes to sense neurotransmitters released by neurons and also communicate with neighboring neurons through the action of gliotransmitters. Previous studies have suggested that a major mechanism mediating gliotransmitter release is vesicular exocytosis evoked by elevations in intracellular [$Ca^{2+}$]. However, the molecular pathways and sources of $Ca^{2+}$ signaling involved in generating these $Ca^{2+}$ elevations remain poorly understood. Here, we investigate the mechanisms governing $Ca^{2+}$-dependent signaling and release of gliotransmitters in hippocampal astrocytes. Our results indicate that astrocytes exhibit store-operated $Ca^{2+}$ entry (SOCE) mediated by $Ca^{2+}$ release-activated $Ca^{2+}$ (CRAC) channels. SOCE is abolished in astrocytes from transgenic mice lacking the canonical CRAC channel proteins Orai1 or STIM1. Furthermore, store-operated $Ca^{2+}$ signals activated through metabotropic purinergic and glutamatergic receptors are abolished in CRAC channel knockout mice. These findings indicate that CRAC channels encoded by Orai1 and STIM1 are a major route of $Ca^{2+}$ entry in hippocampal astrocytes. Using bioluminescence assays, we found that activation of SOCE stimulates ATP secretion from astrocytes, which is dependent on $Ca^{2+}$ influx through CRAC channels. Using the styryl dye FM1-43 to track

exocytosis, we found that activating SOCE by store-depletion or purinergic agonists stimulates vesicular exocytosis in astrocytes. Exocytosis is blocked by inhibitors of SNARE cleavage (botulinum toxins) and by loading cells with BAPTA, consistent with a $Ca^{2+}$-dependent vesicular mechanism of release. Furthermore, genetic deletion of Orai1 expression significantly attenuates vesicular exocytosis in astrocytes. Together, our results show that CRAC channels regulate the $Ca^{2+}$ excitability of astrocytes and play a critical role in regulating gliotransmitter exocytosis. Because gliotransmitters are thought to actively modulate synaptic transmission, the regulation of gliotransmitter release by CRAC channels may have important implications for neuron-glia crosstalk and modulation of neuronal network activity.

**Disclosures:** **A.B. Toth:** None. **K. Hori:** None. **M. Prakriya:** None.

**Poster**

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**Title:** The role of store operated CRAC channels in mediating neural stem cell migration

**Authors: *A. K. SHUM**, T. DING, A. BELMADANI, R. MILLER, M. PRAKRIYA
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**Abstract:** Adult neurogenesis persists as a remnant of neurodevelopment that is maintained in two neurogenic niches: the subventricular zone and the subgranular zone of the dentate gyrus. In the normal state of the brain, these two regions source the neural stem cells (NSCs) and their progenitors that migrate to their respective target sites guided by numerous extrinsic factors and gradients of chemoattractants. Similarly in the injured state of the brain, inflammatory mediators and chemokines guide NSCs towards sites of injury where they can form new neurons to replace those lost by damage. The chemokine, SDF1, and its receptor, CXCR4, are important regulatory factors that play an essential role in neurogenesis and progenitor migration. Chemokine signaling, concomitant with $Ca^{2+}$ transients, is necessary for mediating these downstream effector functions. As a multifunctional second messenger, $Ca^{2+}$ can play an instructive role in regulating cellular processes such as migration and differentiation of NSCs into mature neurons and glia. In NSCs, one pathway for $Ca^{2+}$ entry occurs through the opening of store operated $Ca^{2+}$ release-activated $Ca^{2+}$ (CRAC) channels encoded by the STIM1/Orai1 proteins. Understanding the functional relevance of interactions between an important class of extrinsic factors, the chemokines, and CRAC channels will determine to what extent chemokine-CRAC channel signaling is important for NSC migration. Previously, we have shown the role of CRAC channels

in NSCs in mediating proliferation. The goal of this study is to explore the role of CRAC channels for neural stem cell migration using *in vitro* and *in vivo* assays including genetic knockout and pharmacological suppression of CRAC channel expression/function. *In vitro* migration assays using boyden chambers reveal a deficit in the ability of NSCs to migrate in response to SDF1 chemokine gradients. We have also tracked migrating neural progenitors *in vivo*, by virally labeling neurogenic regions in mice with the calcium-sensitive genetically encoded indicator, GCAMP6. Slice $Ca^{2+}$ imaging and immunohistochemistry have revealed that whereas NSCs normally migrate to the olfactory bulb and integrate as differentiated interneurons, NSCs lacking Orai1 terminally differentiate early and fail to migrate completely to their target site. These results suggest store-operated calcium entry through Orai1 is necessary for SDF1 mediated chemotaxis of NSCs in vitro and for proper *in vivo* migration of NSCs to the olfactory bulb.

**Disclosures: A.K. Shum:** None. **T. Ding:** None. **A. Belmadani:** None. **R. Miller:** None. **M. Prakriya:** None.

**Poster**

**469. CNS Co-Transporters**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 469.01/D51

**Topic:** B.05. Transporters

**Support:** CIHR

SIMONS Foundation (SFARI)

**Title:** Native Kcc2 interactome reveals PACSIN1 as a critical regulator of synaptic inhibition

**Authors: *M. A. WOODIN**[1], S. KHADEMULLAH[2], Z. DARGAEI[3], J. CHEVRIER[4], P. UVAROV[5], J. KWAN[6], R. D. BAGSHAW[7], T. PAWSON[7], A. EMILI[6], Y. DE KONINCK[8], V. ANGGONO[9], M. AIRAKSINEN[5], V. MAHADEVAN[10]
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**Abstract:** KCC2 is a neuron-specific $K^+$-$Cl^-$ cotransporter essential for establishing the $Cl^-$ gradient required for hyperpolarizing inhibition. KCC2 is highly localized to excitatory synapses where it regulates spine morphogenesis and AMPA receptor confinement. Aberrant KCC2

function contributes to numerous human neurological disorders including epilepsy and neuropathic pain. Using unbiased functional proteomics, we identified the KCC2-interactome in the mouse brain to determine KCC2-protein interactions that regulate KCC2 function. Our analysis revealed that KCC2 interacts with a diverse set of proteins, and its most predominant interactors play important roles in postsynaptic receptor recycling. The most abundant KCC2 interactor is a neuronal endocytic regulatory protein termed PACSIN1 (SYNDAPIN1). We verified the PACSIN1-KCC2 interaction biochemically and demonstrated that shRNA knockdown of PACSIN1 in hippocampal neurons significantly increases KCC2 expression and hyperpolarizes the reversal potential for $Cl^-$. Overall, our global native-KCC2 interactome and subsequent characterization revealed PACSIN1 as a novel and potent negative regulator of KCC2.

**Disclosures:** **M.A. Woodin:** None. **S. Khademullah:** None. **Z. Dargaei:** None. **J. Chevrier:** None. **P. Uvarov:** None. **J. Kwan:** None. **R.D. Bagshaw:** None. **T. Pawson:** None. **A. Emili:** None. **Y. De Koninck:** None. **V. Anggono:** None. **M. Airaksinen:** None. **V. Mahadevan:** None.

**Poster**

**469. CNS Co-Transporters**

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**Topic:** B.05. Transporters

**Support:** Human Frontier Science Program

Fondation pour la Recherche Médicale

INSERM

Univ. Pierre et Marie Curie (doctoral fellowship to MG)

**Title:** KCC2 regulates neuronal excitability and hippocampal rhythmogenesis via direct interaction with Trek-2

**Authors: M. GOUTIERRE**[1,2], S. AL AWABDH[1,2], D. GOMEZ-DOMINGUEZ[3], E. FRANÇOIS[1,2], L. M. DE LA PRIDA[3], *J. PONCER[1,2]
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**Abstract:** In mature neurons, the activity of the K-Cl transporter KCC2 plays an essential role in chloride homeostasis and thereby influences GABAergic transmission. Down-regulation of KCC2 has been reported in a variety of neurological and psychiatric conditions and is usually

thought to perturb neuronal activity through altered GABAergic transmission. However, KCC2 also interacts with various molecular partners including actin-related proteins and postsynaptic glutamate receptors. Thus, suppression of KCC2 expression triggers several opposing changes in synaptic function through chloride transport dependent and independent mechanisms. How these effects may combine to alter network activity and lead to the emergence of pathological activities remains difficult to predict.
Using viral-based chronic knock-down of KCC2 in rat hippocampal dentate gyrus, we observed very little effect on the strength of the GABAergic transmission in granule cells (GCs). Perforated patch recordings showed that the shift in EGABA induced by KCC2 suppression was almost fully compensated by a depolarization of the resting membrane potential. We explored the underlying mechanisms for this effect and identified a previously unknown interaction between KCC2 and the leak-potassium channel Trek-2. Thus, loss of KCC2 expression leads to a reduced expression of leak potassium currents and increased membrane excitability in hippocampal GCs. This resulted in an increased EPSP/spike coupling and enhanced recruitment of dentate GCs upon stimulation of entorhinal afferents. Increased GC excitability was associated with alterations of hippocampal rhythmogenesis, with enhanced theta-band activity power during specific behavioral states as detected in ECoG recordings.
Our results reveal a broad and critical role of KCC2 in the control of hippocampal circuit function through a variety of actions on synapses and intrinsic excitability. We propose that down-regulation of KCC2 expression in cortical neurons may result in alterations of rhythmic activities associated with cognitive functions and behavior. Our results suggest that diuretics that act solely to restore neuronal chloride concentration may not fully compensate for the loss of KCC2 under pathological conditions.

**Disclosures: M. Goutierre:** None. **S. Al Awabdh:** None. **D. Gomez-Dominguez:** None. **E. François:** None. **L.M. De La Prida:** None. **J. Poncer:** None.

**Poster**

**469. CNS Co-Transporters**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 469.03/D53

**Topic:** B.05. Transporters

**Support:** Human Frontier Science Program

Fondation pour la Recherche Medicale

INSERM

UPMC doctoral fellowship to CS

**Title:** Chronic KCC2 extinction in mouse dorsal hippocampus compromises contextual memory

**Authors: *C. SIMONNET**[1,2], M. GOUTIERRE[1,2], Y. KOUIDRI[1,2], I. MOUTKINE[1,2], S. DAUMAS[3,4], J.-C. PONCER[1,2]
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**Abstract:** GABA is the main inhibitory neurotransmitter in the adult brain, and provides fast inhibitory neurotransmission mostly through activation of GABAA receptors. As these receptors are mainly permeable to chloride ions, mechanisms controlling chloride homeostasis directly influence GABAergic transmission. In mature cortical neurons, intracellular chloride concentration is controlled by the activity of neuronal chloride/potassium co-transporter KCC2, the expression of which is down-regulated in several neurological and psychiatric conditions associated with cognitive impairment. In the pathology, KCC2 suppression may compromise network activity through alterations of GABA signaling and rhythmogenesis that underlie memory encoding and consolidation. In addition, recent studies revealed ion transport-independent functions of KCC2 at excitatory synapses. Thus, chronic KCC2 down-regulation in hippocampal neurons impairs both the efficacy and long-term potentiation of glutamatergic synapses through modifications of actin dynamics in dendritic spines. We therefore asked whether chronic down-regulation of KCC2 may impact cognitive performances in mice and explored the underlying mechanisms.
Using a viral-based, chronic extinction by RNA interference, we suppressed KCC2 expression in the dorsal hippocampus of adult mice and tested hippocampal LTP, learning and memory 2-4 weeks post-infection. Chronic KCC2 suppression impaired LTP both at perforant path synapses onto granule cells and Schaffer collateral synapses onto CA1 neurons. Next, we tested the behavioral impact of chronic KCC2 suppression in several hippocampus-dependent and independent memory tasks. In a fear conditioning paradigm, we found that contextual memory was specifically compromised upon KCC2 suppression in dorsal hippocampus while cued memory was intact. Next we asked whether these deficits primarily depend on alteration of GABAergic vs. glutamatergic signaling using overexpression of a dominant-negative peptide of KCC2. This approach allows us to specifically disrupt KCC2 interaction with protein partners without affecting its ion transport function. However this did not lead to detectable deficits in contextual memory, suggesting these did not primarily depend on KCC2 transport-independent functions.
We conclude that KCC2 down-regulation in the dorsal hippocampus compromises contextual memory, through mechanisms that remain to be fully explored. Strategies aiming to stabilize KCC2 membrane expression or restore chloride homeostasis may then prove beneficial in rescuing cognitive impairments in conditions associated with KCC2 down-regulation.

**Disclosures: C. Simonnet:** None. **M. Goutierre:** None. **Y. Kouidri:** None. **I. Moutkine:** None. **S. Daumas:** None. **J. Poncer:** None.

**Poster**

**469. CNS Co-Transporters**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 469.04/D54

**Topic:** B.05. Transporters

**Title:** Expression, purification and characterization of full length 12 transmembrane helix potassium chloride cotransporter KCC2

**Authors: *Q. WANG**[1], M. AGEZ[2], P. SCHULTZ[3], I. MEDINA[4], D. BAKER[5], M. BURNHAM[5], R. CARDARELLI[6], L. CONWAY[6], K. GARNIER[2], S. GESCHWINDNER[7], A. GUNNARSSON[7], E. MCCALL[5], A. FRECHART[3], S. AUDEBERT[8], T. DEEB[6], S. MOSS[9], N. BRANDON[1], N. DEKKER[7], A. JAWHARI[2]
[1]Neurosci., Astrazeneca R&D Boston, Waltham, MA; [2]Calixar, Lyon, France; [3]Inst. de Génétique et de Biologie Moléculaire et Cellulaire INSERM, Illkirch, France; [4]INMED INSERM, Marseille, France; [5]Discovery Sci. Astrazeneca, Cambridge, United Kingdom; [6]AstraZeneca Tufts Lab. for basic and translational Neurosci., Boston, MA; [7]Discovery Sci. AstraZeneca, Molndal, Sweden; [8]Aix Marseille Univ, CNRS, INSERM, Marseille, France; [9]Neurosci., Tufts Univ., Boston, MA

**Abstract:** Driven by the high intracellular $K^+$ concentrations maintained by $Na^+/K^+$ ATPase, K-Cl co-transporter KCC2 transports $K^+$ and $Cl^-$ out of cells. KCC2 is expressed almost exclusively in neurons where its proper function is required to maintain low intracellular $Cl^-$ concentrations that are crucial for the inhibitory neurotransmissions of γ-Aminobutyric acid (GABA) and glycine. Loss-of-function mutations of KCC2 cause a severe refractory epileptic encephalopathy in infants. The important role of KCC2 in controlling neuronal excitability is conserved in mice. KCC2 deficits cause frequent seizures in mice and resulted death. Here we examined the transporter activity of variously tagged KCC2 in mammalian cells and successfully solubilized and purified non-aggregated full-length KCC2. The purified KCC2 was characterized biochemically and with electron microscopy. The specific binding of KCC2 inhibitors to the purified KCC2 was demonstrated by surface plasmon resonance (SPR). Our study revealed important features of the molecular architecture of KCC2.

**Disclosures: Q. Wang:** None. **M. Agez:** None. **P. Schultz:** None. **I. Medina:** None. **D. Baker:** None. **M. Burnham:** None. **R. Cardarelli:** None. **L. Conway:** None. **K. Garnier:** None. **S. Geschwindner:** None. **A. Gunnarsson:** None. **E. McCall:** None. **A. Frechart:** None. **S. Audebert:** None. **T. Deeb:** None. **S. Moss:** None. **N. Brandon:** None. **N. Dekker:** None. **A. Jawhari:** None.

**Poster**

**469. CNS Co-Transporters**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 469.05/D55

**Topic:** B.05. Transporters

**Title:** KCC2 modulates spontaneous network events in the perinatal rat and mouse hippocampus

**Authors: M. PUSKARJOV**[1], I. HIIRONNIEMI[1], A. SPOLJARIC[1], M. MAVROVIC[1], P. UVAROV[1], *K. KAILA[2]
[1]Univ. of Helsinki, Helsinki, Finland; [2]Univ. Helsinki, SF-00014 Helsinki, Finland

**Abstract:** The neuron specific K-Cl cotransporter KCC2 is the main $Cl^-$ extrusion mechanism in central neurons. Progressive up-regulation of KCC2 in neocortical and hippocampal principal neurons is known to take place during the first few postnatal weeks in altricial rodents such as the mouse and rat. In more precocious species such as the guinea pig, up-regulation of KCC2 and thus maturation of functionally inhibitory $GABA_AR$-mediated postsynaptic signaling in principal neurons is shifted towards life in utero. Functional up-regulation of KCC2 has been suggested to act as the key signal for ending the period of trophic GABA actions in brain development. Here we show using bidirectional pharmacological manipulation of KCC2 activity that this developmentally regulated $Cl^-$ transporter has an important role in controlling spontaneous network events already in the perinatal hippocampus of rats and mice.

**Disclosures: M. Puskarjov:** None. **I. Hiironniemi:** None. **A. Spoljaric:** None. **M. Mavrovic:** None. **P. Uvarov:** None. **K. Kaila:** None.

**Poster**

**469. CNS Co-Transporters**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 469.06/D56

**Topic:** B.05. Transporters

**Support:** Uppsala University

**Title:** Membrane Bound SNAT10 (SLC38A10) regulates Mammalian Target of Rapamycin(mTORC1) Signaling under varied cellular stress

**Authors:** *R. TRIPATHI[1], ***R. TRIPATHI**[1], *R. TRIPATHI[1], T. AGGARWAL[2], K. NORDENANKAR[2], F. LINDBERG[2], R. FREDRIKSSON[2]
[1]Dept. of Pharmaceut. Biosci., Uppsala Univ., Uppsala, Sweden; [2]UPPSALA University/Department of Pharm Biosci., Uppsala, Sweden

**Abstract:** The mammalian target of rapamycin, mTOR (serine/threonine kinase) controls various functions in the cell such as cell growth and metabolism. Deregulation of mTOR has resulted into numerous human diseases for example cancer, obesity and diabetes. mTOR is composed of two different functional units, mTORC1 and mTORC2. mTORC1 is the main target of rapamycin and essentially regulates different biochemical reactions such as protein, lipid synthesis and autophagy which results into controlling cellular homoeostasis. Hence regulation of mTORC1 is crucial for cellular growth and development. mTORC1 functionality is controlled by energy levels, nutrients, and growth factors. Among this amino acids have emerged as a major regulator for mTORC1. The cellular metabolisms are regulated by various membrane transport proteins which mediate the transport of nutrient molecules across cell membranes. Solute carriers (SLCs) are one of the largest classes of membrane-bound transporter proteins. In neuronal cells various SLCs monitor numerous cellular processes, including the role of transporters for amino acids between cells and for neurotransmitter cycling. The SLC38 family includes eleven members and is also called sodium-coupled neutral amino acid transporters (SNATs). Members of the SLC38 family such as SLC38A2 and SLC38A9 act as mTOR sensors and regulate mTOR signaling cascade in response to different external stress. Different amino acids act as source of providing energy for intracellular protein turn over, nutrient transport through the plasma membrane, cell growth, migration as well as maintenance of cell integrity. The major goal of this study is to determine the in vitro function of SNAT10 in mTORC1 regulation and physiology using conditional knock out (KO) mice. We have discovered differences at the basal intracellular amino acid pool between SNAT10 KO primary neuronal cells. Under nutrient stress, SNAT10 KO cells showed increased concentrations of aspartic acid, glutamine and glutamine acid and a decreased basal level of total mTOR protein. We also investigated the role of SNAT10 under different cellular stress responses both oxidative stress and glutamate excitotoxicity. The knockout SNAT10 mice were subjected to different behavioral paradigms, including rotarod, beam walk, elevated plus maze and marble burying test where we investigated t the basal motor, cognitive and emotional behavior of the mice.

**Disclosures:** **R. Tripathi:** A. Employment/Salary (full or part-time):; Uppsala University. **T. Aggarwal:** A. Employment/Salary (full or part-time):; UPPSALA UNIVERSITY. **K. Nordenankar:** A. Employment/Salary (full or part-time):; UPPSALA UNIVERSITY. **F. Lindberg:** A. Employment/Salary (full or part-time):; UPPSALA UNIVERSITY. **R. Fredriksson:** A. Employment/Salary (full or part-time):; Uppsala University.

**Poster**

**469. CNS Co-Transporters**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 469.07/D57

**Topic:** B.05. Transporters

**Support:** Vetenskapsrådet, Swedish Research Foundation

Novo Nordisk fonden

Åhlén-stiftelsen

Hjärnfonden, Swedish Brain Foundation

**Title:** Defining solute carrier distribution and function in the central nervous system

**Authors: *N. N. SCHWEIZER**, S. BAGCHI, R. FREDRIKSSON
Pharmaceut. Biosci., Uppsala Univ., Uppsala, Sweden

**Abstract:** Directed transport of nutrients, particularly amino acids, is a prerequisite for cell survival. This is to a large extent done by SLCs. Different SLC transporters are known to overlap in substrate specificities and in cellular location, and thus provide a redundancy in the systems they are involved in. For example, within the SLC38 family, several members likely constitute a yet unexplored regulatory network involved in the control of protein synthesis. Research on SLC transporters is often hampered by compensatory effects that mask the effect of a genetic or pharmacological intervention performed on one SLC. In a systematic approach to resolving global SLC distribution throughout the brain by high-throughput single-cell RNA sequencing we aim to map the co-expression of different SLC transporters with neuronal markers identifying neuronal types, such as excitatory vs. inhibitory or interneurons, in different anatomical structures throughout the mouse brain. The large data set generated through systematic single-cell RNA sequencing can potentially serve as basis for research on SLC functional compensation and ultimately to targeting SLCs in a more directed manner during pharmacological intervention in disease.

**Disclosures: N.N. Schweizer:** None. **S. Bagchi:** None. **R. Fredriksson:** None.

**Poster**

**469. CNS Co-Transporters**

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**Topic:** B.05. Transporters

**Support:** NIH Grant RO1 NS051445-08

**Title:** Transcriptional regulation of the system $x_c^-$ light chain, xCT, in astrocytes

**Authors: *Y. HE**, C. P. ROSSER, J. SHI, J. A. HEWETT, S. J. HEWETT
Dept. of Biol., Syracuse Univ., Syracuse, NY

**Abstract:** The activity of system $x_c^-$ ($Sx_c^-$), a hetereomeric plasma membrane amino acid transporter, critically regulates intracellular glutathione synthesis/maintenance and extracellular glutamate levels in the central nervous system. In astrocytes, interleukin 1β (IL-1β), a prototypical inflammatory factor upregulated in various neurological diseases/disorders, facilitates $Sx_c^-$ expression via transcriptional (Jackman et al. 2010) and post-transcriptional (Shi et al. 2016) control of *Slc7a11*, the gene that encodes for the substrate specific light chain, xCT. While we reported that HuR mediates stabilization of astrocyte xCT mRNA following IL-1β treatment (Shi et al. 2016), the mechanism underlying transcriptional control has yet to be identified. IL-1β signals canonically through NF-κB and p38 MAPK pathways and non-canonically via a variety of other kinase systems. Thus, in this study we examined the potential signaling pathways by which IL-1β regulates xCT expression transcriptionally using pharmacological selective inhibitors. Primary mouse astrocytes were treated for 30-60 min with selective inhibitors of IκB kinase β (20 μM TPCA-1), p38 MAPK (10 μM SB 203580), PI3K (25 μM LY 294002), AKT (5 μM Akti-1/2), protein kinases A and C (20 μM H-7), or to a pan PKC inhibitor (1 μM Go 6983), followed by addition of IL-1β (3 ng/ml). Lysate samples were harvested 4 hr later and xCT mRNA expression levels measured via quantitative PCR. We found that the IL-1β-mediated increase in xCT expression was effectively attenuated by TPCA-1, SB 203580, LY 294002, H-7 but not Go 6983 or Akti-1/2, implicating involvement of NFκB, p38 MAPK, PI3K and PKA, but not PKC and AKT. Thus, our results reveal multiple layers of regulation of xCT expression in astrocytes by IL-1β signaling.

**Disclosures: Y. He:** None. **C.P. Rosser:** None. **J. Shi:** None. **J.A. Hewett:** None. **S.J. Hewett:** None.

**Poster**

**469. CNS Co-Transporters**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 469.09/D59

**Topic:** B.05. Transporters

**Title:** Activation of AKT increases cell surface expression of System $x_c^-$

**Authors: *P. VERSLUIS**, A. GIBSON, M. SCHMIDT, D. SMITH, L. CHASE
Biochem., Hope Col., Holland, MI

**Abstract:** System $x_c^-$ is a heterodimeric plasma membrane transporter involved in the exchange of intracellular glutamate for extracellular cystine. As such, this transporter plays a critical role in the production of the antioxidant glutathione. Previous studies in our lab have demonstrated that there is an increase in cell surface expression within ten minutes of exposure to $H_2O_2$ in confluent U138MG human glioma cells. The study described herein sought to begin to characterize the mechanism by which $H_2O_2$ regulates the trafficking of xCT. We hypothesized that Akt signaling is necessary for $H_2O_2$-mediated trafficking of of xCT. A significant increase in Akt phosphorylation was observed in U138MG cells following ten-minute exposure to 3 mM $H_2O_2$ compared to vehicle-treated cells using western blot analysis. Treatment with the Akt inhibitor 10-DEBC (2.5µM) for 30 minutes prior to and during $H_2O_2$ exposure resulted in a decrease in $H_2O_2$-induced phosphorylation of Akt at Ser473. Similar inhibition of Akt phosphorylation at Thr308 was observed following treatment of cells with 1.0µM API-2. Next, we used simultaneous treatment of cultured glioma cells with both inhibitors in the presence of $H_2O_2$ and observed a reduction in the trafficking of endogenously expressed xCT to the plasma membrane. To determine if the regulation of xCT cell surface expression is not limited to human glioma cells, we also studied the role Akt plays in the trafficking of recombinant, transiently-expressed xCT in COS-7 cells. COS-7 cells transfected with myc-tagged xCT, 4F2HC and a constitutively active form of Akt showed higher levels of xCT localized to the membrane compared with cells transfected with a dominant negative form of Akt. Collectively, these data suggest that Akt is an important regulator of xCT cell surface expression. We are currently using a mutagenesis approach to determine if phosphorylation of xCT at putative Akt phosphorylation sites is necessary for increased cell surface localization of xCT.

**Disclosures: P. Versluis:** None. **A. Gibson:** None. **M. Schmidt:** None. **D. Smith:** None. **L. Chase:** None.

**Poster**

**469. CNS Co-Transporters**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 469.10/D60

**Topic:** B.05. Transporters

**Title:** Regulation of System $x_c^-$: Effects of N-terminal and C-terminal mutations on xCT cell surface expression

**Authors: A. GIBSON**, P. VERSLUIS, M. SCHMIDT, *L. A. CHASE
Hope Col., Holland, MI

**Abstract:** System $x_c^-$ exchanges intracellular glutamate for extracellular cystine across the membrane of many cell types, including astrocytes. Its activity directly regulates the synthesis of the antioxidant glutathione and the extracellular concentration of glutamate in some areas of the brain. Dysregulation of the transporter can lead to excessive glutamate release and excitotoxic cell death or the depletion of glutathione stores and the development of oxidative stress. We recently demonstrated that oxidants acutely upregulate System $x_c^-$ activity by triggering the rapid redistribution of the transporter from intracellular compartments to the cell surface. Our current work suggests that the trafficking of the transporter may be regulated by ubiquitination and that oxidant exposure directly influences the ubiquitination of the transporter. Since increased ubiquitination tends to decrease the cell surface expression of many membrane transporters, we sought to test the hypothesis that System $x_c^-$ is ubiquitinated and that the ubiquitination status of the transporter regulates both its cell surface expression and activity. We have used a mutagenesis approach to disrupt putative ubiquitination sites and a putative ubiquitin ligase binding site within a myc-tagged System $x_c^-$ construct so that we can understand the role ubiquitination plays in regulating the cell surface expression of System $x_c^-$. There are seven highly conserved lysine residues within xCT that are located on the cytoplasmic side of the membrane. These residues are located at positions 4, 37, 41, 43, 422, 472, and 473. We have created mutant forms of this construct containing single or multiple lysine to arginine mutations so that we could assess the effect of these mutations on cell surface expression of System $x_c^-$. Using biotinylation assays and immunocytochemical analysis, we have demonstrated that mutation of the N-terminal lysine residues increases the cell surface expression of the transporter. We are currently assessing the ubiquitination status of these mutant transporters to determine if the changes in ubiquitination are associated with changes in the cell surface expression and activity of the transporter. In addition, we have identified a putative ubiquitin ligase binding site in the C-terminus of the transporter. Our preliminary studies suggest disruption of this binding site also leads to an increase in cell surface expression of the transporter. Collectively, these data suggest that System $x_c^-$ is regulated by changes in its

ubiquitination status such that factors which lead to diminished ubiquitination will allow for increased cell surface expression of the transporter.

**Disclosures:** **A. Gibson:** None. **P. Versluis:** None. **M. Schmidt:** None. **L.A. Chase:** None.

**Poster**

**469. CNS Co-Transporters**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 469.11/D61

**Topic:** B.05. Transporters

**Support:** 5R01NS052634-10

**Title:** Extracellular matrix modulates system $x_c^-$ (SXC) mediated glutamate release from gliomas via CD44

**Authors: *J. MARTIN**[1,2], S. M. ROBERT[2], R. A. UMANS[2], H. SONTHEIMER[2]
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**Abstract:** Significant aberrations in biological function arise in glial-derived malignant tumors known as glioblastoma multiforme (GBM), many of which confer treatment resistance. An example found in GBM is the upregulation of a splice variant of the cell surface glycoprotein CD44, which correlates negatively with survival of patients and tumor-bearing mice. CD44 is a putative co-receptor of the cystine/glutamate antiporter system $x_c^-$ (SXC) that is upregulated in approximately half of GBM patients. SXC imports cystine for the synthesis of glutathione (GSH), an important intracellular antioxidant that confers protection from reactive oxygen species (ROS), as well as radiation and chemotherapy. In exchange for cystine, SXC releases glutamate into the peritumoral brain. When upregulated, SXC function results in assiduous glutamate release, creating an excitotoxic environment for surrounding neurons. We hypothesize that CD44 plays a role in regulating SXC function through stabilization of xCT, the catalytic subunit of the antiporter, in the cell membrane. This stabilization contributes to an increased number of functional SXC transporters, and as a result, increased cystine uptake, GSH synthesis, and enhanced resistance to oxidative stress. To test this hypothesis, we confirmed a putative interaction between CD44 and xCT. First, immunostaining of cells and tumor-bearing tissue slices revealed co-localization of CD44 and SXC on the cell membrane. Second, antibodies bound to CD44 immunoprecipitate xCT and vice versa, suggesting a physical interaction between CD44 and xCT. To determine whether CD44 regulates SXC function, we used a fluorometric glutamate assay to quantify glutamate release from SXC-expressing GBMs after treatment with siRNA against CD44. Knockdown of CD44 reduced glutamate release by half, compared to control cells. The addition of the CD44 ligand Hyaluronic acid (HA) to the medium for 24 hours caused a significant increase in glutamate release into the medium of CD44

expressing cells; conversely, incubation with the HA-degrading enzyme Hyaluronidase (HYAL) decreased glutamate release to sub-control levels. This regulation suggests a normal regulatory role for CD44 on SXC function. Consistent with this notion, extracellular HA expression correlates positively with xCT expression. These studies suggest that SXC is modulated by extracellular matrix activation via CD44, which provides an additional therapeutic target to reduce SXC function.

**Disclosures: J. Martin:** None. **S.M. Robert:** None. **R.A. Umans:** None. **H. Sontheimer:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.01/D62

**Topic:** B.07. Synaptic Transmission

**Support:** ANR-10-JCJC-1406

**Title:** Anterior thalamic nuclei provide excitation and PV mediated feed-forward inhibition onto presubicular layer 3 neurons

**Authors: M. NASSAR**[1], J. SIMONNET[2], B. MATHON[3], L.-W. HUANG[4], I. COHEN[5], M. BENDELS[6], R. MILES[7], *D. FRICKER[8]
[1]Inst. Du Cerveau Et De La Moelle Epiniere, Paris, France; [2]Bernstein Ctr. for Computat. Neurosci., Humboldt Univ. zu Berlin, Berlin, Germany; [3]Inst. du Cerveau et de la Moelle, Paris, France; [4]Univ. of Edinburgh, Edinburgh, United Kingdom; [5]INSERM U1130 / CNRS UMR8246 / UPMC, Paris, France; [6]Univ. Aachen, Aachen, Germany; [7]Insitut du Cerveau et de la Moelle, Paris, France; [8]UMR8119, CNRS, Paris, France

**Abstract:** The presubiculum contains head direction cells which are crucial for spatial navigation. Here, we explored the functional connectivity of the thalamic head directional input to superficial layer 3 neurons of the mouse presubiculum with double patch-clamp recordings, retrograde tracing and optogenetics. A viral vector containing channelrhodopsin-2 (ChR2) and a fluorescent reporter protein was injected in anterior thalamic nuclei (ATN). Presubicular slices were sectioned after 10 to 20 days. We found that ATN densely innervated superficial layers 1 and 3 of the presubiculum. Excitatory synaptic events were reliably recorded following photostimulation of ChR2 transfected ATN fibers in pyramidal neurons located in layer III of presubiculum. We show that presubicular pyramidal neurons projecting to medial entorhinal cortex were directly contacted, and synaptic responses persisted in the presence of TTX and 4AP. ATN fibers also directly excited fast spiking, parvalbumin expressing (PV) interneurons but not low threshold spiking, somatostatin expressing (SST) interneurons in layer 3 of

presubiculum. ATN-mediated excitation of pyramidal neurons was typically followed by a disynaptic inhibitory component probably due to feedforward inhibition. We show a high connectivity between presubicular pyramidal neurons and PV interneurons. Finally, we demonstrate optogenetic silencing of PV interneurons suppressed feedforward inhibition of principal neurons, confirming these interneurons are the major source of feedforward inhibition. Our data point to a distinct role of presubicular interneurons in head-direction tuning.

**Disclosures:** **M. Nassar:** None. **J. Simonnet:** None. **B. Mathon:** None. **L. Huang:** None. **I. Cohen:** None. **M. Bendels:** None. **R. Miles:** None. **D. Fricker:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.02/D63

**Topic:** B.07. Synaptic Transmission

**Support:** AMRF 1116016

**Title:** Internal excitatory network in the subthalamic nucleus: An optogenetic functional mapping investigation

**Authors:** ***P. S. FREESTONE**[1], K. L. TODD[1], J. LIPSKI[2]
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**Abstract:** The basal ganglia is a sub-cortical structure receiving a wide range of inputs almost from the entire brain. As such, it is involved in motor control, learning, memory and reward-driven behaviour. The subthalamic nucleus (STN), a major glutamatergic nucleus of the basal ganglia projecting to the substantia nigra pars reticulata (SNr) and pars compacta (SNc) nuclei, plays a crucial role in the *indirect* and *hyperdirect* pathways. Previous electrophysiological studies suggest that STN neurons also make internal synapses through axon collaterals with other glutamatergic neurons in the nucleus. Our aim is to apply the optogenetic technique of functional mapping to rapidly detect and investigate the connectivity between neurons within the STN, and to identify excitatory inputs through such collaterals. CD-1 mice expressed channelrhodopsin (H134R) under the CaMKIIα promotor after injection of the viral (AAV5) construct into the STN. Neuronal activity was monitored using whole-cell patch-clamp electrophysiological recordings from horizontal ventral midbrain slices (250 µm) containing the STN, SNr and SNc after 4-8 weeks expression. Functional mapping was conducted using a digital mirror device (*Polygon400*, MightEx) to sequentially illuminate squares (20-80 $\mu m^2$) of a grid (800 x 600 µm) in a pseudorandom fashion, while recording post-synaptic currents from single neurons. Using this approach, we have shown that focal photo-stimulation (6 $mW/mm^2$, 5 ms) at multiple discrete locations within the STN can evoke currents recorded from a single STN neuron. These

light-evoked currents are delayed (2-4 ms relative to the onset of photo-stimulation), and comprise of multiple peaks, confirming they are not due to direct activation of ChR2 in the recorded neuron. It remains to be investigated the exact nature of these internal glutamatergic connections within the STN, and what role they might have in determining the activity of their downstream projections.

**Disclosures: P.S. Freestone:** None. **K.L. Todd:** None. **J. Lipski:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.03/E1

**Topic:** B.07. Synaptic Transmission

**Support:** NIMH R00 4R00MH099243-03

Whitehall foundation

**Title:** Mapping projection populations to striatal neurons

**Authors: *K. CHOI**[1,2], E. N. HOLLY[1,2], M. F. DAVATOLHAGH[3], K. BEIER[4], M. FUCCILLO[2]
[2]Dept. of Neurosci., [3]Dept. of Neuroscience, Neurosci. Grad. Group, [1]Univ. of Pennsylvania, Philadelphia, PA; [4]Stanford Univ., Stanford, CA

**Abstract:** The dorsomedial striatum (DMS) receives afferent inputs from cortex, thalamus and midbrain, and has been implicated in reward-sensitive motor behaviors. It is presently unclear whether projection neuron populations exhibit specific connectivity to the diverse cell types within the DMS - a key point in understanding the computations performed by these circuits during choice behaviors. We compared the anatomical and physiological connectivity of projection neurons that synapse on three major DMS cell types - D1 spiny projection neurons (SPN), and parvalbumin (PV) and somatostatin (SST) interneurons - using cell-type specific rabies virus tracing and optogenetic-mediated projection neuron recruitment. Starter cell populations were labeled with Cre-sensitive TVA expression via injection into either D1-Cre, PV-2a-Cre or SST-ires-Cre mice. After injection with pseudotyped rabies virus-EGFP, all starter cell populations demonstrated robust numbers of retrogradely labeled neurons originating in the orbitofrontal cortex, anterior cingulate/secondary motor cortex (ACC/M2), thalamus and globus pallidus externus. Despite subtle target cell-dependent differences for OFC and specific thalamic nuclei, we found similar numbers of retrogradely labeled neurons per starter cell for each postsynaptic target. While rabies virus methods have been regularly used to assess cell type-specific anatomical connectivity, it is unclear how these data correspond to physiological

measures of connectivity. To test this, we focused on the ACC - a major projection population to the DMS exhibiting no differences in anatomical connectivity. To quantitatively compare synaptic properties and postsynaptic recruitment as a function of input, we normalized the number of recruited afferent ACC fibers via the “optical component” of the striatal field while recording whole cell configuration in nearby genetically-labeled D1, PV and SST cells. Despite the similar anatomical connectivity by viral tracing, we found significant differences in excitatory synaptic strength, with PV interneurons exhibiting the strongest ACC synapses, followed by D1 SPNs, then SST interneurons. Differences in synaptic strength between ACC-PV and ACC-D1 SPN synapses resulted largely from synapse structure, while the weakness of ACC-SST synapses was a mixed effect of small release site number, low release probability and decreased postsynaptic responsiveness. Taken together, this suggests a model for striatal projection neuron connectivity in which postsynaptic cell type largely imposes diversity of physiological connectivity on a “skeleton" of non-specific anatomical connectivity.

**Disclosures: K. Choi:** None. **E.N. Holly:** None. **M.F. Davatolhagh:** None. **K. Beier:** None. **M. Fuccillo:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.04/E2

**Topic:** B.07. Synaptic Transmission

**Support:** NIMH Grant MH66123

**Title:** Morphological complexity of human substantia nigra synapses

**Authors: *S. J. MABRY**, J. K. ROCHE, R. C. ROBERTS
Psychiatry/Behavioral neurobiology, Univ. of Alabama Birmingham, Birmingham, AL

**Abstract:** The substantia nigra and ventral tegmental area (SN/VTA) are the largest dopaminergic nuclei in the brain and receive glutamatergic and GABAergic inputs that regulate dopaminergic neuronal activity. Abnormal dopamine transmission is affected in several diseases, most notably Parkinson’s disease and schizophrenia. While the cytoarchitecture, connectivity and neurotransmitter content of the SN/VTA has been examined extensively, especially in animal models, ultrastructural data in human SN/VTA is scarce. We examined 7 control cases: 4M&3F, 2AA&5C, 39.7±15.0 years, PMI=6.0±1.3 hours. Synapses in the vicinity of dopamine neurons were photographed in serial sections. In most parts of the brain, including human postmortem striatum and cortex, synapses can easily be characterized by the morphology of the postsynaptic density (PSD) into type 1 (thick PSD) and or type II (thin PSD), which correspond to excitatory and inhibitory neurotransmission, respectively. However, in the SN/VTA synaptic

morphology was much more complex, with many synapses containing a presynaptic density of varying shape and thickness. We identified six types of type 1 synapses, five types of type II synapses and synapses with intermediate PSDs. In synapses with presynaptic densities, these were thin or thick, and/or solid or elaborately irregular. PSDs were thin, thick or intermediate and solid or elaborately irregular. There were 1.119±0.173 mitochondria per axon terminal with similar numbers in classic type 1 or type II synapses. Recent studies have shown that neurons in the SN/VTA contain multiple transmitters, and use more than one transmitter in a given synapse which could lead to the variability in synaptic morphologies.

**Disclosures: S.J. Mabry:** None. **J.K. Roche:** None. **R.C. Roberts:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.05/E3

**Topic:** B.07. Synaptic Transmission

**Support:** the Henry G. Leong Professorship in Neurology (SLH); the Donation Fund for Neurology Research (SLH), Health

Medical Research Fund, Food and Health Bureau, Hong Kong.

**Title:** Localization and functional study of synaptic vesicle protein synaptogyrin3 (SYNGR3) on dopaminergic neuronal system and its potential link to Nurr1

**Authors: *L. LI**[1], P. HO[1], H. LIU[1], Z. TSE[1], C. LAM[1], M. LEUNG[1], M. KUNG[1], D. B. RAMSDEN[2], S. HO[1]
[1]Dept. of Medicine, Li Ka Shing Fac. of Med., The Univ. of Hong Kong, Hong Kong, Hong Kong; [2]Inst. of Metabolism and Systems Research, Univ. of Birminghm, Bermingham, United Kingdom

**Abstract: Background:** SYNGR3 is an integral synaptic vesicle protein in the synaptogyrin family. Among the three isoforms of synaptogyrin (SYNGR1-3), SYNGR3 is specifically expressed in brain. However, the physiological function of SYNGR3 in neurons is unknown. Previous studies have shown that SYNGR3 can physically interact with DAT protein [1]. Intracellular DA, if not properly sequestered, will undergo auto-oxidation leading to oxidative stress. Furthermore, we identified three non-canonical Nurr1 response elements (NBRE, AGGTCA) in 5’ flanking region of SYNGR3 gene. Nurr1 is an orphan nuclear receptors belonging to the transcription factor superfamily, which promotes differentiation and survival of dopaminergic (DA) neurons [2]. Therefore, we hypothesize that SYNGR3 has a role in dopaminergic neurons to facilitate dopamine re-take for vesicle packaging and dopamine

recycling, and Nurr1 may influence this process via regulating SYNGR3 expression.
**Method and Results:** Immunogold EM revealed that SYNGR3 was co-localized in close proximity with DAT in the striatal synaptic termini. Immunoprecipitation of DAT using anti-DAT antibody resulted in co-precipitation of SYNGR3 from mouse striatal lysates, and vice versa. Overexpression of SYNGR3 in SH-SY5Y cells caused significant increase in cellular DA uptake activity as compared with empty-vector controls. EMSA showed that Nurr1 proteins bound specifically to the three NBREs in the 5' flanking region of human SYNGR3 gene.
**Conclusion:** We demonstrated that overexpressing SYNGR3 in neuronal cells increased DA uptake efficiency, possibly via strengthening interaction between synaptic vesicles and DAT on the plasma membrane. Co-localization of SYNGR3 and DAT in striatal synapses may have functional significance to maintain DA homeostasis for normal motor movement and cognitive functions. Nurr1 may influence this process via regulating SYNGR3 expression.
**References**
1. Egaña, L.A., et al., *Physical and functional interaction between the dopamine transporter and the synaptic vesicle protein synaptogyrin-3.* The Journal of Neuroscience, 2009. **29**(14): p. 4592-4604.
2. Decressac, M., et al., *NURR1 in Parkinson disease--from pathogenesis to therapeutic potential.* Nat Rev Neurol, 2013. **9**(11): p. 629-36.

**Disclosures: L. Li:** None. **P. Ho:** None. **H. Liu:** None. **Z. Tse:** None. **C. Lam:** None. **M. Leung:** None. **M. Kung:** None. **D.B. Ramsden:** None. **S. Ho:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.06/DP02/E4 (Dynamic Poster)

**Topic:** B.08. Synaptic Plasticity

**Title:** The connectome of newly born neurons

**Authors: *G. WILDENBERG**[1], N. B. KASTHURI[2]
[1]Univ. of Chicago/Argonne Natl. Lab., Chicago, IL; [2]Neurobio., Univ. of Chicago, Chicago, IL

**Abstract:** A clear promise of stem cell therapy is rewiring malfunctioning brains by replacing damaged neurons with new neurons derived from stem cells (SCNs). However, little is known about the functional endpoint of how neural stem cells establish synapses with each other and with pre-existing neurons. Current attempts to evaluate the efficacy of stem cell derived neuron (SCN) synapse formation rely on techniques that reveal only a small fraction of SCN synapses (<<1%) and little about the role of non-neuronal cells (e.g. astrocytes, microglia, etc.) in this process. We have developed a multi-scale imaging pipeline to identify and track SCN differentiation and integration into existing networks of neurons over complete brains. We will

couple synchrotron source micro X-ray tomography (μXCT) techniques unique to Argonne National Labs with our pipeline for automated serial electron microscopy (EM) ('connectomics'). We will use genetic labeling strategies to visualize and distinguish stem cells, their neuronal progeny, and their synapses from 'host' neurons and synapses in both EM and X-ray datasets. We will use this staining to allow seamless integration and traversal between sub-micron mapping of SCNs location over entire brains with μXCT and subsequent targeted reconstruction of their connectivity with nanometer scale EM. Ascertaining the 'rules' by which SCNs integrate into neuronal networks could reveal cellular and subcellular targets for increasing the therapeutic efficiency of SCNs as well as reveal fundamental processes by which neurons develop and make synapses in the brain.

**Disclosures: G. Wildenberg:** None. **N.B. Kasthuri:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.07/E5

**Topic:** B.07. Synaptic Transmission

**Support:** NIH K01MH107760

**Title:** Mechanisms by which the prefrontal cortex distinguishes ventral hippocampal from mediodorsal thalamic inputs

**Authors: *E. TEBOUL**[1], S. CANETTA[1,2], S. S. BOLKAN[2], N. PADILLA COREANO[3], C. KELLENDONK[2,1]
[1]New York State Psychiatric Inst., New York, NY; [2]Columbia Univ., New York, NY; [3]MIT, Cambridge, MA

**Abstract:** The prefrontal cortex (PFC) serves as a hub for cognitive and affective behaviors including spatial working memory and anxiety. Two major sources of information to the PFC are provided by the ventral hippocampus (vHPC) and the mediodorsal thalamus (MD), both of which provide glutamatergic input to this structure. Despite this convergence of input, optogenetically silencing either the vHPC to PFC or MD to PFC inputs produces distinct behavioral responses. For example, silencing vHPC to PFC terminals decreases anxiety (Padilla-Coreano N et al, Neuron, 2016) and selectively impairs encoding of spatial working memory (Spellman T et al, Nature, 2015) while silencing MD to PFC terminals does not affect anxiety and instead selectively impairs maintenance of spatial working memory (Bolkan S et al, Nature Neuroscience, 2017). However, the mechanisms by which the prefrontal cortex is able to selectively distinguish between seemingly identical neurotransmitter inputs to generate behaviorally distinct responses is unknown.

To address this, we used optogenetics in combination with slice electrophysiology in the PFC to assess the functional connectivity and efficacy of synaptic transmission for both projections under different input frequencies. Using virally-delivered blue- or red-light activated ChR2 (Chronos and Chrimson, respectively), we investigated whether vHPC and MD cells project to the same PFC pyramidal cells and parvalbumin-expressing (PV) interneurons, and whether synaptic transmission from these two projections is differentially affected by input frequency. We found that all layer II/III PFC pyramidal cells sampled received input from the MD and from the vHPC. However, while all PV interneurons sampled received input from the MD, only a portion received input from the vHPC. We also found that MD versus vHPC inputs onto pyramidal cells could be distinguished based on their frequency-specific synaptic dynamics and that these differed from what was seen at synaptic inputs onto PV cells. Future experiments will examine functional connectivity and synaptic dynamics at MD and vHPC inputs onto other genetically defined interneuron populations as well as how these inputs to the PFC may be altered in an environmental risk factor model for schizophrenia with known PFC dysfunction.

**Disclosures: E. Teboul:** None. **S. Canetta:** None. **S.S. Bolkan:** None. **N. Padilla Coreano:** None. **C. Kellendonk:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.08/E6

**Topic:** B.07. Synaptic Transmission

**Support:** KIST grant 2E26190

KIST grant 2E26170

NIH Grant U01NS099691

**Title:** Mapping of excitatory and inhibitory activities of distinct neuronal populations in hippocampal slices using ArcLight

**Authors: *R. NAKAJIMA**, T. GEILLER, B. J. BAKER
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**Abstract:** To understand the brain circuitry, it is essential to clarify the functional connectivity among distinct neuronal populations. By using associated adeno virus in combination with cre-lox system, we expressed a genetically encoded voltage indicator, ArcLight, in specific neuronal populations of mouse hippocampus. The expression of ArcLight was limited either in $Ca^{2+}$/calmodulin-dependent protein kinase II alpha (CaMK2a) excitatory neurons or in parvalbumin (PV) interneurons in the CA1 hippocampus. We then observed the fluorescence

change of ArcLight by electrically stimulating Schaffer collateral in hippocampal CA1 region of slice preparations under fast-CCD camera. In excitatory neurons, ArcLight could detect glutamatergic depolarization as well as GABAergic hyperpolarization. On the other hand, we found that PV interneurons were strongly inhibited by voltage-gated potassium channels. In contrast to GCaMP6f which only detected excitatory responses, ArcLight could detect both excitatory and inhibitory responses from specific cell populations. ArcLight and similar probes are becoming a powerful paradigm for functional connectivity mapping of brain circuitry.

**Disclosures: R. Nakajima:** None. **T. Geiller:** None. **B.J. Baker:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.09/E7

**Topic:** B.01. Neurotransmitters and Signaling Molecules

**Support:** Intramural NICHD award to CJM

**Title:** Developmental characterization of hippocampal VGluT3-expressing interneurons

**Authors: C. FANG**, G. VARGISH, T. EKINS, K. AUVILLE, D. CALVIGIONI, R. CHITTAJALLU, *K. A. PELKEY, C. J. MCBAIN
NICHD/LCSN, NIH, Bethesda, MD

**Abstract:** Cholecystokinin expressing interneurons (CCK-INTs) are positioned to powerfully influence hippocampal information processing by providing strong feedforward and feedback inhibition to principal cells (PCs). However, despite a wealth of information describing intricate synaptic details of CCK-INTs (eg. depolarization induced suppression of inhibition (DSI)/asynchronous release (AR)), their network functions remain enigmatic. This relates to the fact that, beyond common developmental origins and CCK expression, CCK-INTs comprise a heterogeneous cohort with unique postsynaptic target preferences and molecular signatures. Interestingly, one subset of CCK-INTs, vesicular glutamate transporter 3- (VGluT3) expressing perisomatic targeting CCK basket cells ($VGluT3^+$CCKBCs), was recently shown to critically regulate theta oscillations and spatial information coding of place cells. Initial reports of VGluT3 expression within this subpopulation prompted speculation that $VGluT3^+$CCKBCs subserve unique computational roles based on their ability to co-release GABA and glutamate. Indeed, in contrast to Dale's principal of "one neuron, one transmitter" recent studies have described a variety of central neurons that utilize more than one classical neurotransmitter including GABA/glutamate co-releasing neurons in subcortical circuits. However, detailed investigation into the functional properties of a pure $VGluT3^+$ CCK-INT cohort, including glutamate release, is currently lacking. We initiated a developmental characterization of $VGluT3^+$ INTs using

VGluT3Cre:Ai14 reporter mice. As expected a large percentage of reported INTs have perisomatic targeting axons with cannabinoid receptor 1 (CBR1) labeled terminals, typical of CCKBCs. Surprisingly, however, the population extends beyond VGluT3$^{+}$CCKBCs to include subsets of dendrite targeting INTs. VGluT3 expression, revealed by both cell reporting and terminal VGluT3 staining, is very low at early postnatal ages and then increases through development, plateauing around P30. Preliminary electrophysiological interrogation of VGluT3Cre:Ai14 reported stratum radiatum INTs revealed basic membrane/spiking properties consistent with CCK-INTs. Moreover, paired recordings with CA1 pyramidal cells in juvenile mice revealed that GABAergic transmission from VGluT3$^{+}$CCKBCs exhibits similar unitary synaptic properties to VGluT3$^{-}$CCKBCs, including DSI and AR. Further investigations will probe for unique synaptic properties of VGluT3$^{+}$ INTs that promote participation in spatial information coding and may contribute to siezure phenotypes following loss of VGluT3.

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**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.10/E8

**Topic:** B.07. Synaptic Transmission

**Title:** Pathway-specific recruitment of inhibition in motor cortex

**Authors: *J. J. COUEY**[1], B. M. HOOKS[2]
[2]Dept. of Neurobio., [1]Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

**Abstract:** Primary motor cortex (M1) is required for purposeful movement and skill learning. To better understand M1 function, we aim to determine the anatomical and microcircuit basis for integration of different sources of incoming information within M1. We have previously shown that pyramidal cells in M1 receive unique innervation patterns from cortical and thalamic inputs. Here, using a combination of optogenetics and electrophysiology, we analyze the functional projections from cortical and thalamic input sources to primary motor cortex (M1) interneurons. We used parvalbumin (PV) and somatostatin (SOM) Cre-driver mouse lines to fluorescently label interneuron subpopulations and target them for whole cell patch clamp recordings. Stereotactic injections were used to express opsins selectively in axons from primary somatosensory cortex (S1) or sensory thalamus (PO). In acute brain slices, stimulation of labelled axons during whole-cell recordings from PV+ and SOM+ interneuron subpopulations revealed interneuron sub-type specific projection patterns from both S1 and PO that differ from the targeting of nearby pyramidal neurons. PV+ interneurons receive complementary patterns of input from S1 and PO. In contrast, SOM+ interneurons receive substantially different input.

These results support the hypothesis that feedforward inhibition via PV+ interneurons is recruited in a pathway specific manner. In contrast, SOM+ interneurons are potentially recruited by the local circuitry with a primary role in facilitating local competition between groups of activated pyramidal cells and PV+ interneurons.

**Disclosures: J.J. Couey:** None. **B.M. Hooks:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.11/E9

**Topic:** B.07. Synaptic Transmission

**Support:** European Union's Horizon 2020 > research and innovation programme under grant agreement No. 720270

**Title:** A comprehensive protein- Protein interaction map of the mammalian synaptic proteome

**Authors: *O. SOROKINA**, C. MCLEAN, K. F. HEIL, E. WYSOCKA, M. D. R. CRONING, D. C. STERRATT, S. G. GRANT, T. I. SIMPSON, J. D. ARMSTRONG
The Univ. of Edinburgh, Edinburgh, United Kingdom

**Abstract:** The presynaptic and postsynaptic compartments mediate neurotransmitter release and its perception via a series of complex and highly dynamic networks of protein-protein interactions. The identification of protein candidates for synapses has been a major priority since appropriate high-throughput methods were first established, with the first synaptic proteome studies published around the turn of the century. We examined synaptic proteome studies focusing on the mammalian brain from 2000 to present, which spans a period of rapid technological development and refinement in proteomics.
We combined 30 major synaptic proteomic studies (21 post synaptic and 9 presynaptic) to obtain a list of 6500 genes. We retrieved protein-protein interactions (PPIs) for the combined list of proteins and constructed the most complete PPI networks to date for presynaptic and postsynaptic compartments. We studied the network properties and identified the community structure of our pre- and post-synaptic PPI networks against a non-exhaustive set of commonly available clustering algorithms. Exploiting network based measures semi-local *centrality* and cluster *Bridgeness* we identified topologically important proteins that can simultaneously influence remote clusters in addition to their immediate locality.
We also tested the obtained network structure of the pre- and post-synaptic proteomes for enrichment of common neurological and neurodevelopmental diseases and disorders including: Schizophrenia (SCH), Alzheimer's disease (AD), Autistic Spectrum Disorder (ASD), Autistic Disorder (AUT), Bipolar Disorder (BD), Hypertension (HT), Epilepsy Syndrome (Epi),

Parkingson's Disease (PD), Frontotemporal Dementia (FD), Huntington's Disease (HD) and Intellectual Disability (ID) as defined within the Human Disease Ontology (HDO). Besides the clear links between the identified network substructures and specific diseases we found evident difference in disease susceptibility of pre- and post-synaptic compartments.

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**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.12/E10

**Topic:** B.08. Synaptic Plasticity

**Support:** NHMRC Grant APP1083209

**Title:** Developmental profiling of the actin-associated protein tropomyosin at central nervous system synapses

**Authors: *T. FATH**, A. K. SUCHOWERSKA, E. C. HARDEMAN, P. W. GUNNING
Sch. of Med. Sci., Univ. of New South Wales, Sydney, Australia

**Abstract:** The actin cytoskeleton in the post-synaptic compartment of synapses is crucial to supporting synaptic maturation, structure and function. The family of tropomyosins are one of many actin-associated proteins known to regulate the postsynaptic actin cytoskeleton and are considered as gate keepers of actin filament dynamics. We have previously shown the spatial segregation to the pre- and post- synapse of different tropomyosin isoforms at central nervous system synapses, indicative of specific regulation of actin filament populations in different subcellular compartments. Here, we biochemically confirm previous reports of a segregation of Tpm1.12 to the pre-synaptic compartment and Tpm4.2 to the post-synaptic compartment. We also show that in C57Bl6 wild-type mice, there is a developmental shift in the expression of tropomyosin isoforms: as the total pool of Tpm4.2 in the brain decreases with age, there is an increase in localisation of Tpm4.2 to the post synaptic compartment in aged mice. Together these data demonstrate the instrumental role of Tpm4.2 in regulating the post synaptic actin cytoskeleton, particularly in aged mice.

**Disclosures: T. Fath:** None. **A.K. Suchowerska:** None. **E.C. Hardeman:** None. **P.W. Gunning:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.13/E11

**Topic:** B.08. Synaptic Plasticity

**Support:** German Research Council (DFG, SFB 1089)

BONFOR

**Title:** Fluorescent proteins for 2P FLIM analysis of presynaptic protein interactions

**Authors: *P. GULAKOVA**[1], D. DIETRICH[2], S. SCHOCH[1]
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**Abstract:** Dynamic protein-protein interactions are essential for the regulation of synaptic transmission and plasticity. To understand these interactions and correlate them to functional changes it is necessary to resolve them in live neurons. 2-photon (2P) fluorescence lifetime imaging (FLIM) of Förster resonance energy transfer (FRET) is a powerful tool to study such interactions and provides the necessary temporal and spatial resolution even in native tissue. However, there are certain requirement on pairs of fluorescent proteins (FPs) to be used e.g. a high FRET efficiency and photon yield in the presynaptic compartment, sufficiently separate 2P excitability and a lifetime of the donor being ideally monoexponential and insensitive to fusion to target proteins.
Here we examined a list of cyan-yellow and red-green FP pairs (linked with a flexible linker, $SRG_4SG_4S$) for their suitability for 2P-FLIM-FRET studies in neurons. Expressing FPs in HEK293T cells proved to be inapplicable as their rapid division caused a significant fraction of immature red proteins, which did not act as acceptors and lead to a strong underestimation of FRET efficiency. This effect was not seen when transducing primary neurons with FPs and analysing FRET efficiencies at DIV 13-17.
We quantified FRET for the following FP pairs by measuring the reduction in donor lifetimes: mNeon-mRFP/TagRFP/mCherry2, TagRFP-mNeon, mEGFP-mRFP/TagRFP/mCherry2, Clover-mRuby2, mTurquoise2-Ypet/Venus/mOrange2/mNeon, mCerulean-Ypet/Venus, mTFP1-Ypet/Venus/mOrange2.
Most donors in the absence of acceptors displayed monoexponential lifetimes, while mCerulean showed a biexponential fluorescent decay. Donors fused to acceptors, in every case showed biexponential lifetimes, which for most green-red pairs could be explained by the presence of 2 fractions of pairs – one undergoing FRET and the other one not. FRET efficiencies for the tested pairs ranged from 39% to 72%, mNeon-mRFP and mTurquoise2-Ypet displayed the most pronounced FRET efficiencies being 58% and 72%, respectively. These strong FRET effects were confirmed in native neurons of hippocampal mouse brain slices after viral transduction *in*

*vivo*. Furthermore, the fluorescent properties and FRET efficiencies of these proteins were unaffected by fusion to presynaptic proteins and targeting to the presynaptic compartment. Taken together, mNeon-mRFP and mTurquoise2-YPet appeared to be highly suited for 2PFLIM-FRET studies in neurons with the former being advantageous for distinguishing changes in fluorophore distances from changes in the fraction of interacting molecules and the latter showing an outstandingly high FRET efficiency.

**Disclosures: P. Gulakova:** None. **D. Dietrich:** None. **S. Schoch:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

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**Topic:** B.07. Synaptic Transmission

**Support:** IBS-R002-D1

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**Title:** SALM4 suppresses excitatory synapse development by cis-inhibiting trans-synaptic SALM3-LAR adhesion

**Authors: *E. LIE**[1], J. KO[2], S.-Y. CHOI[3], J. D. ROH[3], Y. CHO[4], R. NOH[5], D. KIM[3], Y. LI[3], H. KANG[6], T.-Y. CHOI[7], J. NAM[8], W. MAH[4], D. LEE[9], S.-G. LEE[10], H. KIM[10], H. KIM[9], S.-Y. CHOI[7], J. UM[6], M.-G. KANG[5], Y. BAE[4], J. KO[2], E. KIM[1,3,8]
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Korea Univ., Seoul, Korea, Republic of; [10]Grad. Sch. of Med. Sci. and Engineering, KAIST, Daejeon, Korea, Republic of

**Abstract:** Synaptic adhesion molecules regulate synapse development, function, and plasticity. These functions mainly involve trans-synaptic interactions and positive regulations, whereas cis interactions and negative regulation are less understood. Here we report that SALM4, a member of the SALM family of synaptic adhesion molecules, suppresses excitatory synapse development through cis inhibition of SALM3, another SALM family protein with synaptogenic activity. *Salm4*-mutant (*Salm4*$^{-/-}$) mice show increased excitatory synapse numbers in the hippocampus. SALM4 cis-interacts with SALM3, inhibits trans-synaptic SALM3 interaction with presynaptic LAR family receptor tyrosine phosphatases, and suppresses SALM3-dependent presynaptic differentiation. Importantly, deletion of Salm3 in *Salm4*$^{-/-}$ mice (*Salm3*$^{-/-}$;*Salm4*$^{-/-}$) normalizes the increased excitatory synapse number. These results suggest that SALM4 negatively regulates excitatory synapses via cis inhibition of the trans-synaptic SALM3-LAR adhesion.

**Disclosures: E. Lie:** None. **J. Ko:** None. **S. Choi:** None. **J.D. Roh:** None. **Y. Cho:** None. **R. Noh:** None. **D. Kim:** None. **Y. Li:** None. **H. Kang:** None. **T. Choi:** None. **J. Nam:** None. **W. Mah:** None. **D. Lee:** None. **S. Lee:** None. **H. Kim:** None. **H. Kim:** None. **S. Choi:** None. **J. Um:** None. **M. Kang:** None. **Y. Bae:** None. **J. Ko:** None. **E. Kim:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.15/F1

**Topic:** B.07. Synaptic Transmission

**Title:** Molecular organization at the synapse by cryo-electron tomography

**Authors: A. MARTINEZ-SANCHEZ**, Z. KOCHOVSKI, U. LAUGKS, C. PAPANTONIOU, W. BAUMEISTER, *V. LUCIC
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**Abstract:** The composition and the state of molecular complexes are the major determinants of their function. Cryo-Electron Tomography allows high resolution, comprehensive imaging of complexes within their natural environment. However, cellular complexity and molecular heterogeneity has prevented their structural detection. We have developed a novel image processing method for detection and classification of macromolecular structures present in cellular cryo-electron tomograms. The application to tomograms of neocortical rodent synaptosomes showed that despite a large variety, many synaptic complexes fall into distinct classes. Our quantitative analysis showed that these classes posses a distinct spatial distribution at a single nanometer scale, but also that this organization is flexible. Finally, the combination of

structural features and localization of the complexes points to their molecular identity and their roles in the synaptic transmission.

**Disclosures: A. Martinez-Sanchez:** None. **Z. Kochovski:** None. **U. Laugks:** None. **C. Papantoniou:** None. **W. Baumeister:** None. **V. Lucic:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 470.16/F2

**Topic:** B.07. Synaptic Transmission

**Support:** EMBO ALTF 70-2015

LTFCOFUND2013, GA-2013-609409

**Title:** Functional mapping of a synaptic adhesive code in neurons

**Authors: *A. M. GOMEZ**[1], L. TRAUNMÜLLER[1], P. SCHEIFFELE[2]
[1]Univ. of Basel, Basel, Switzerland; [2]Biozentrum Univ. Basel, Basel, Switzerland

**Abstract:** Neurons integrate tens of thousands of diverse inputs organized in distinct domains along their extensively branched and stereotyped dendritic tree. A synaptic adhesion code proposes to assemble complex circuits, yet a small fraction of the genome encodes for synaptic adhesion proteins. Alternative splicing bypasses the low coding power of the genome by expanding the molecular diversity required to assemble trillions of synapses into complex networks. We recently discovered that Slm2 - an RNA-binding protein - drives a highly dedicated alternative splicing program for the specification of glutamatergic synapses in the hippocampus. Remarkably, the Slm2-dependent program targeted to a devoted splice site of all three Neurexin pre-mRNAs. Here we test the idea that this Slm2-dependent synaptic specification tunes the functional integration of synaptic inputs either by uniform or clustered presentation of cell-type specific Neurexin isoforms on individual axons. By using functional imaging and electrophysiology we have mapped the distribution and strength of synaptic input coordinate with differential neurexin isoform expression.

**Disclosures: A.M. Gomez:** None. **L. Traunmüller:** None. **P. Scheiffele:** None.

**Poster**

**470. Synaptic Connectivity: Organization and Function**

**Location:** Halls A-C

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**Program#/Poster#:** 470.17/F3

**Topic:** B.07. Synaptic Transmission

**Title:** Paired pulse facilitation and depression of intrinsic synaptic connectivity in the claustrum of the fruit bat, Carollia perspicillata

**Authors: *R. ORMAN**[1], S. E. FOX[3], M. G. STEWART[2]
[1]Physiology&Pharmacology, [2]Physiol. & Pharmacol., SUNY Downstate Med. Ctr., Brooklyn, NY; [3]Dept Physiol & Pharmacol, State Univ. of New York Downstate Med. Ctr., Brooklyn, NY

**Abstract:** Carollia perspicillata is a member of the new-world leaf-nosed bat family. Carollia's claustrum contains cells whose intrinsic excitatory circuitry is sufficient to: (1) generate single, spontaneous, synchronized burst discharges in disinhibited brain slices, (2) support activity spread along the axes where claustral cells are aligned, and (3), because of multiple axes for cell alignment, support activity spread along both the rostro-caudal and the dorso-ventral axes (Orman et al., JCN 2017 525:1459-1474) in contrast to the discrete cellular alignment shown in rats (Orman, J Physiol Sci 2015 65:533-44). We used a paired pulse paradigm to explore excitatory and inhibitory synaptic connectivity in Carollia brain slices on a 64 electrode grid. Simultaneous field potential responses were recorded throughout claustrum. Events evoked by stimuli applied to the overlying neocortex included (1) an initial brief antidromic population spike followed by (2) a population EPSP of about 5 ms duration associated with increased spiking activity, and finally (3) an IPSP of about 20 ms duration. Single conditioning pulses or short conditioning pulse trains (2-5 pulses) revealed frequency potentiation of EPSPs that persisted for 200 ms or longer. The maximal facilitation appeared to occur at about 100 ms after a conditioning pulse train. Interestingly, the population IPSP, while initially facilitated (within the first 30 ms), was subsequently depressed for periods of 200 ms or longer. The amount of depression increased as more pulses were included in the train. These results are consistent with the time course of GABA-A receptor desensitization (e.g. Jones and Westbrook, Neuron 1995 15: 181-191). Spontaneous unit activity was increased during this period of EPSP facilitation and IPSP depression. These results extend the characterization of the intrinsic connectivity of the bat claustrum. The EPSP properties closely resemble the frequency potentiation described in other brain regions, such as hippocampus (e.g. Fox and Ranck, Exp Brain Res 1981 41:399-410; Kunitake et al. Hippocampus 2004 14:986-999) and improve our understanding of the intrinsic excitatory connectivity of the bat claustrum. The properties of the synaptic circuits, both excitatory and inhibitory, highlight the richness of the set of synaptic changes available to modulate the region's intrinsic connectivity.

**Disclosures:** **R. Orman:** None. **S.E. Fox:** None. **M.G. Stewart:** None.

**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

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**Program#/Poster#:** 471.01/F4

**Topic:** B.08. Synaptic Plasticity

**Support:** NIH R01 DK61935 (MJT)

**Title:** Identification of hypothalamic proteins involved in hormone-independent activation of progestin receptors by dopamine

**Authors:** ***K. D. ACHARYA**[1], S. A. NETTLES[1], C. F. LICHTI[2], L. DENNER[3], M. J. TETEL[1]
[1]Neurosci. Program, Wellesley Col., Wellesley, MA; [2]Dept. of Pathology and Immunol., Washington Univ. Sch. of Med., St. Louis, MO; [3]Dept. of Intrnl. Med., Univ. Texas Med. Br., Galveston, TX

**Abstract:** Progesterone is required for neural development, neuroprotection, sexual differentiation and reproduction. Progesterone mediates many of these effects through its receptors, progestin receptor (PR)-A and PR-B. In the female hypothalamus, estrogens induce PR expression, which is essential for the expression of reproductive behavior. While progesterone binding to PR can facilitate lordosis in females, this behavior can also be mediated by dopamine activation of hypothalamic PR in the absence of hormone. In the present study, we sought to identify proteins involved in hormone-independent activation of PR by dopamine in the hypothalamus. Eight week old C57BL6 mice were ovariectomized, and a week later subcutaneously injected with estradiol benzoate (EB, 1 µg) to induce PR. Forty-eight hours following EB injection, mice were infused with 100 ng of SKF, a D1 receptor agonist, or vehicle into the 3$^{rd}$ ventricle. Thirty minutes after the SKF infusion, mice were sacrificed, hypothalami were collected and proteins were extracted. Protein-protein pull-down assays were done using recombinant GST-tagged mouse PR-A or PR-B in the presence or absence of R5020, a PR agonist. Isolated protein complexes from SKF- or vehicle-treated tissue that interacted with unliganded PR were analyzed by tandem mass spectrometry. We identified hypothalamic proteins that interacted with PR-A in an SKF-dependent manner, the majority of which were synaptic regulators, components of neuronal cytoskeleton and kinases. A significant number of identified proteins that interacted with unliganded PR-A were associated with regulation of energy metabolism, transcription and translation. In contrast to PR-A, unliganded PR-B did not associate with any detected hypothalamic proteins in an SKF-dependent manner, suggesting that PR-A contributes more than PR-B to the hormone-independent activation of mouse PR by dopamine, which is consistent with previous behavioral studies. The identified interactome of dopamine-activated PR provides mechanisms by which the receptor can be activated in the

absence of hormone by a ligand-independent mechanism. Additionally, the current findings offer further evidence for differential mechanisms of PR-A and PR-B action in neuronal function and behavior. Finally, these findings provide hormone-independent mechanisms of PR activation that may be involved in female reproductive health and energy homeostasis. Current studies are further exploring the dopamine-dependent PR interactome using reverse phase protein arrays and mass spectrometry-based phosphoproteomics.

**Disclosures: K.D. Acharya:** None. **S.A. Nettles:** None. **C.F. Lichti:** None. **L. Denner:** None. **M.J. Tetel:** None.

**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 471.02/F5

**Topic:** B.08. Synaptic Plasticity

**Support:** Telethon-Italy GGP11043

Compagnia di San Paolo ROL-4318

**Title:** Inter-synaptic lateral diffusion of GABAA receptors shapes inhibitory synaptic currents

**Authors: *E. PETRINI**, T. RAVASENGA, E. DE LUCA, A. POLENGHI, T. NIEUS, A. BARBERIS
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**Abstract:** The lateral mobility of neurotransmitter receptors has been reported to tune synaptic signals. However, whether receptor diffusion may functionally connect two distinct synapses remains unclear. The present study provides evidence for a novel mechanism of synaptic crosstalk based on the diffusion of desensitized GABAA receptors (GABAARs) between inhibitory synapses. Indeed, by combining single particle tracking and laser photolysis of caged neurotransmitter, we demonstrate that upon synaptic activation, GABAARs can diffuse between adjacent dendritic GABAergic synapses in long-living desensitized states. As a consequence of the larger abundance of desensitized GABAA receptors at the receiving synapse, synaptic responses are transiently reduced. Glutamatergic activity (mimicked by optogenetic LiGluK2 activation) limits this inter-synaptic diffusion by trapping GABAARs at excitatory synapses. We also demonstrate that the functional cross-talk among neighboring synapses described here is calcium-dependent. Overall those data demonstrate that a given inhibitory synapse may modulate neighboring inhibitory synapses by spreading the “memory” of its recent activation. This novel form of activity-dependent hetero-synaptic interplay is likely to modulate synaptic signaling and

is expected to refine dendritic synaptic integration and enhance neuronal computational capabilities.

**Disclosures:** **E. Petrini:** None. **T. Ravasenga:** None. **E. de Luca:** None. **A. Polenghi:** None. **T. Nieus:** None. **A. Barberis:** None.

**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

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**Program#/Poster#:** 471.03/F6

**Topic:** B.08. Synaptic Plasticity

**Support:** Loyola University Chicago Faculty Startup Fund (AU:104832)

Ministry of Science and Technology, Taiwan (106-2917-I-010-004)

Loyola University Chicago Provost Fellowship

**Title:** Real-time mapping of the sensory homunculus by applying pseudorandomly coded peripheral nerve stimulation

**Authors: *V. C.-F. CHEN**[1], W.-W. YANG[2], L.-L. PAN[2], M. CMIEL[1], L.-W. CHOU[2]
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**Abstract:** Clinical researchers have long considered the task of localizing real-time changes in the cortical areas that handle sensory signals a difficult one, primarily due to limitations of biomedical instrumentation. The electroencephalogram (EEG), despite providing excellent temporal resolution for monitoring real-time brain signals, can only offer very limited spatial resolution of brain activities. This makes it difficult to determine the origins of brain signals, which in turn makes it challenging to pinpoint the exact cortical areas that are actively functioning. In the proof of concept for this study, EEG signals acquired from a young male subject are segmented into appropriate epochs based on a pseudorandom binary sequence. During EEG acquisition, peripheral nerve stimulation synchronized with the same pseudorandom binary sequence is applied to the immediate surface of the subject's right median nerve, enabling us to perform calculations of autocorrelation values derived from the pseudorandom binary sequence and the power spectral density of the EEG epochs. Higher autocorrelation values provide greater certainty as to the origin of the brain signals. By utilizing features of this stochastic method, we can provide close to real-time brain maps that can accurately associate ever-changing cortical activities with indications of neuroplasticity. This innovation can be utilized as a groundbreaking tool for navigated transcranial magnetic stimulation (TMS)

applications. Our study was carried out in accordance with the ethical principles for human medical experimentation as set out in the Declaration of Helsinki.

**Disclosures: V.C. Chen:** None. **W. Yang:** None. **L. Pan:** None. **M. Cmiel:** None. **L. Chou:** None.

**Poster**

**471. Short-Term Plasticity**

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**Program#/Poster#:** 471.04/F7

**Topic:** B.08. Synaptic Plasticity

**Support:** NIH 1043021101

**Title:** Nmda receptor swapping during synaptic plasticity

**Authors: *D. LI**, D. V. MADISON
Mol. and Cell. Physiol., Stanford Univ., Palo Alto, CA

**Abstract:** NMDA glutamate receptors play a central role in triggering several forms of activity-dependent synaptic plasticity, including long-term potentiation (LTP) and depression (LTD). Here we show that CA3-CA3 synapses between rat hippocampal pyramidal neurons lack detectable GluN2B-containing receptors in their active postsynaptic membrane in basal conditions, but swap to having mostly GluN2B-containing receptors following the induction of either LTP or LTD. These GluN2B receptors source by diffusion from the extrasynaptic membrane, but this receptor swap requires dynamin-dependent endocytosis. This swap does not require that plasticity be successfully induced, but rather depends only on the delivery of the patterned stimulation in an NMDAR-dependent manner. Thus, this swap represents a novel form of metaplasticity, with which a synapse essentially keeps a record of previous activity, regardless of whether a change in synaptic strength occurs. As such, this NMDA receptor swap represents a potential new mechanism for storing memory traces at the synaptic level.

**Disclosures: D. Li:** None. **D.V. Madison:** None.

**Poster**

**471. Short-Term Plasticity**

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**Topic:** B.08. Synaptic Plasticity

**Support:** KY Sci. and Eng 3712- RDE-019

University of KY Office of Undergraduate Research

Deutscher Akademischer Austausch Dienst (DAAD) German Academic Exchange Service. RISE – Program

**Title:** The dependence on nerve evoked conditions in relation to the occurrence of spontaneous quantal events at *Drosophila* neuromuscular junctions

**Authors: *C. R. BALLINGER BOONE**[1], T. DONOVAN[2], R. SHUMARD[2], A. COOPER[2], M. MELODY[2], T. HICKEY[2], C. HERMANNS[2], Z. R. MAJEED[2], M. CORNELIUS[2], H. GARRIGUS[2], E. HIGGINS[2], M. LABARRE[2], A. LARSON[2], M. MCNABB[2], K. MONTICELLO[2], B. STOCKWELL[2], P. BOACHIE[2], A. HO[2], B. SLABACH[2], K. WEINECK[2], M. MEDLEY[2], N. D. PETTERSSON[2], J. MCCALL[2], C. MALLOY[2], R. L. COOPER[2]
[1]Univ. of Kentucky, Walton, KY; [2]Univ. of Kentucky, Lexington, KY

**Abstract:** Synaptic vesicles will spontaneously fuse at synaptic sites with this mechanism related to the $Ca^{2+}$ concentration within the presynaptic nerve terminal. We set out to examine if the occurrence of spontaneous events (minis) after a series of evoked stimulations is correlated to the frequency and duration of a stimulus train. Short-term facilitation at the neuromuscular junctions is due in part to residual $Ca^{2+}$ in the nerve terminal. However, if evoked release from high efficacy synapses result in evoked depression then the limiting factor may be the number of readily release vesicles to sense residual $Ca^{2+}$. Thus a lower frequency in occurrence of these minis may depend on the degree of the evoked synaptic depression. In addition, the frequency in occurrence of minis may also be independent of evoked events if the vesicles that give rise to the events are independent of each other. We hypothesize that the residual $Ca^{2+}$ should affect the frequency of mini occurrence. We analyzed the frequency in occurrences of minis with differing stimulating conditions using the *Drosophila* NMJ. Preliminary data with 20, 40 and 60Hz stimulation of 30 pulses indicates that the nerve terminal is able buffer the internal $Ca^{2+}$ level quickly and not impact the frequency of minis under these conditions. Various other conditions are currently being examined and will be reported on. A better understanding of these events would help to address the residue effect of nerve stimulation on synaptic transmission in various physiological conditions.

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**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

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**Program#/Poster#:** 471.06/F9

**Topic:** B.08. Synaptic Plasticity

**Support:** A2016397S

**Title:** Hp1bp3 influences neuronal excitability and cognitive function

**Authors: *S. DING**, S. NEUNER, K. O'CONNELL, C. KACZOROWSKI
The Jackson Lab., Bar Harbor, ME

**Abstract:** Recently, heterochromatin protein 1 binding protein 3 (*Hp1bp3*) was identified as a novel regulator of cognitive aging using a combination of forward genetics and a global knock-out mouse model. Through gene set enrichment analyses, we discovered that genes whose hippocampal expression correlated with that of *Hp1bp3* were significantly enriched for terms related to plasma membrane localization and for functions related to neuronal excitability. As changes in hippocampal neuronal excitability and plasticity have been posited to underlie learning and memory processes, we hypothesized *Hp1bp3* may be mediating its effects on cognitive aging via the regulation of hippocampal neuronal excitability. To test this hypothesis, we performed a targeted intrahippocampal knockdown of *Hp1bp3* in adult mice, followed by behavioral analyses and slice electrophysiology. Mice receiving shRNA for *Hp1bp3* exhibited both working and contextual fear memory deficits, demonstrating that decrease of *Hp1bp3* in the hippocampus is sufficient to induce cognitive deficits reminiscent of those observed in global knock-out mice. In addition, these mice exhibited decreased hippocampal neuronal excitability as indicated by an increase in the slow after-hyperpolarization (sAHP), providing a candidate mechanism for *Hp1bp3*-mediated changes in cognitive function. As *Hp1bp3* is known to regulate chromatin accessibility and gene expression, it is likely that *Hp1bp3* regulates the expression of critical ion channels and receptors in the plasma membrane. Ongoing work in the lab will examine this question in more detail. Finally, hippocampal sAHP plasticity in disrupted in mouse models of Alzheimer's disease, suggesting *Hp1bp3* may play a role in AD-related cognitive deficits, a possibility which will be investigated in future studies.

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**Poster**

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**Topic:** B.08. Synaptic Plasticity

**Support:** BMBF grant 01EO1401 (German Center for Vertigo and Balance Disorders)

**Title:** How many release sites does a depressing synapse need to optimally transfer information?

**Authors: *M. SALMASI**[1,2,5], S. GLASAUER[1,2,3,5], M. STEMMLER[4,5]
[1]Grad. Sch. of Systemic Neurosciences, [2]German Ctr. for Vertigo and Balance Disorders, [3]Neurol., [4]Biol. II, Ludwig-Maximilians-Universität, Munich, Germany; [5]Bernstein Ctr. for Computat. Neurosci., Munich, Germany

**Abstract:** Chemical synapses transmit information by releasing vesicles packed with neurotransmitter. Synaptic release, however, is not a reliable process, as sometimes action potentials fail to trigger the release, or vesicles are released spontaneously. Synapses employ multiple release sites to compensate for the probabilistic behavior of the release. Here we study how the number of release sites changes the rate of information transfer [1,2] at a synapse during short-term depression. The presynaptic input spike train, *X*, triggers the release at *K* independent release sites of the synapse. It is assumed that the neurotransmitter content of one released vesicle is enough to activate all the receptors on the post-synaptic site. We define an effective release process, *Z*, which is one if at least one of the *K* sites releases a vesicle and is zero otherwise (Fig. 1A). The effective release process corresponds to the EPSP that is recorded from the post-synaptic neuron. Short-term depression is incorporated into our model by assuming that each release site is inactivated after a release and recovers exponentially back to its initial release probability.

We calculate the amount of information about the presynaptic input spike train that a synapse can transfer through its *K* release sites to the post-synaptic neuron (Fig. 1B). When the number of release sites increases, the intermittent unresponsiveness of one release site is compensated by the other sites, and synaptic information transmission is facilitated. However, increasing the number of release sites augments the chance of spontaneous release as well and degrades the information transfer of the synapse. Our analysis determines the optimal number of release sites for each synapse, using the initial evoked and spontaneous release probabilities, recovery time constant and input spike rate of the synapse.

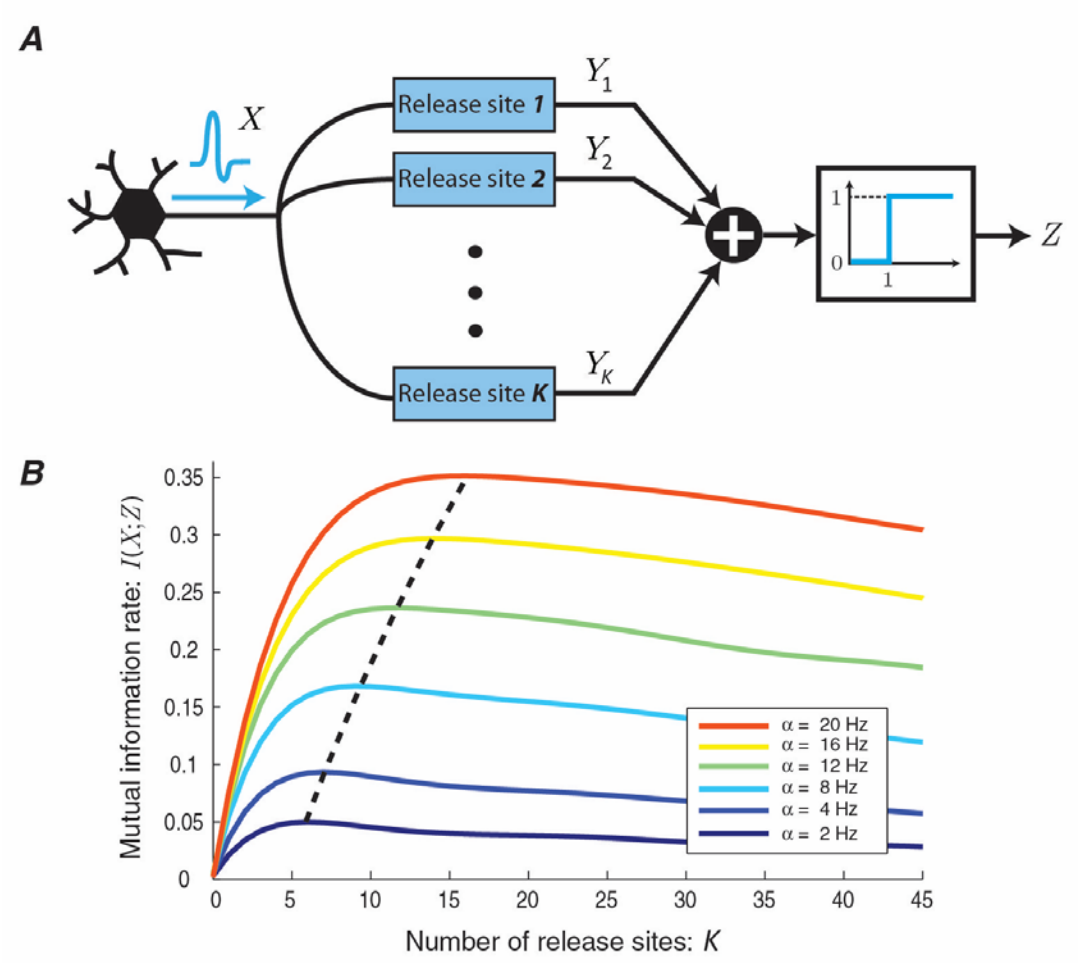


Figure1: A) Information transmission through multiple release sites of one synapse. B) Mutual information rate between the input spike train and the effective release process against the number of release sites, for different input spike rates, α. The dashed black line connects the maximum values.

**Disclosures:** **M. Salmasi:** None. **S. Glasauer:** None. **M. Stemmler:** None.

**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 471.08/F11

**Topic:** B.08. Synaptic Plasticity

**Title:** Dopaminergic effects on optogenetically activated inputs on subcortical and commissural projecting layer V medial prefrontal pyramidal neurons

**Authors: J. M. LEYRER**[1], *M. P. THOMAS[2]
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**Abstract:** The prefrontal cortex renders humans the capability of flexible behavior and mediates working memory tasks. Functionally these regions are homologous to the medial prefrontal cortex (mPFC) in the rodent. The mPFC is known to be targeted by various brain regions, including the contralateral mPFC, the amygdala, the hippocampus and the thalamus, which carry information essential for working memory tasks. However, it remains relatively unknown how information from these inputs is integrated by layer V pyramidal neurons, the major cortical output cells. Additionally, it is well established that optimal levels of dopamine within the prefrontal cortex are required for proper working memory function. In this study, we have characterized the excitatory synaptic responses of contralateral mPFC inputs onto type I (pontine projecting) and type II (commissural projecting) layer V pyramidal cells. Additionally, we identified the effects of dopamine, through both D1 receptor and D2 receptor activation, on these responses. To study isolated inputs, an optogenetic approach, using channelrhodopsin-2, was used to specifically activate commissural inputs targeting the mPFC. Using whole cell patch clamp recordings, synaptic responses were recorded from both type I and type II pyramidal cells identified with green retrobeads based on their projection patterns. A blue LED was used to elicit synaptic responses of commissural fibers expressing channelrhodopsin-2 and mCherry. Initial experiments suggest that contralateral connections onto type I cells always produce facilitating EPSPs. Additionally, D1 receptor activation increases the amplitude of EPSPs, enhances facilitation and increases the rise time and decay time of EPSPs. These results suggest that D1 receptor activation may promote persistent activity within type I cells, facilitating working memory tasks mediated by the mPFC. These experiments may lend insight into how layer V pyramidal cells integrate convergent synaptic inputs, as well as how dopamine may modulate synaptic functions that may contribute to working memory.

**Disclosures: J.M. Leyrer:** None. **M.P. Thomas:** None.

**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

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**Program#/Poster#:** 471.09/F12

**Topic:** B.08. Synaptic Plasticity

**Support:** KY Sci. and Eng. 3712- RDE-019 (RLC)

University of KY Office of Undergraduate Research

Deutscher Akademischer Austausch Dienst (DAAD) German Academic Exchange Service. RISE – Program

**Title:** Examining temporary loss of sensory perception over development in altering long-term function and neural circuitry effects behavioral responses

**Authors: *T. R. DONOVAN**[1], C. BALLINGER BOONE[2], B. SLABACH[2], K. WEINECK[2], M. MEDLEY[2], N. DZUBUK PETTERSSON[2], J. MCCALL[2], E. SOMASUNDARAM[2], C. MALLOY[2], R. COOPER[2]
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**Abstract:** Since Hubel and Wiesel (1963) the effects of sensory deprivation in a developing CNS has been a focus in determining critical periods and the effects on neural circuitry. The ability to temporarily enhance or depress electrical activity in sensory neurons at various stages in development provides cues in understanding the plasticity of the nervous system. Temporarily altering activity of presynaptic neurons can have effects on morphology and function of target cells subsequent to the experimental manipulations. Thus, altered neural circuits may manifest themselves in asymptomatic behaviors to standard sensory cues. We are addressing these topics in the larval Drosophila model over embryonic and larval development. In using genetic approaches, we are controlling activity in sensory systems and examining eating and locomotive behaviors as well as tactile sensory assays. In addressing the effects on neural architecture to correlate with the neural activity conditioning paradigms, sensory endings as well as projections into the CNS are being investigated. We will report on the behavioral responses to tactile stimuli throughout larval develop during various experimental manipulations. We also investigating how a previously deprived neural circuit can regain the ability for normal behavior, anatomical structure and function, providing a novel understanding of the understanding synaptic plasticity within defined neural circuits.This relates to various disease states as well as to exomedicine in the terms of development within weightless of space and as well as re-exposure to gravity.

**Disclosures: T.R. Donovan:** None. **C. Ballinger Boone:** None. **B. Slabach:** None. **K. Weineck:** None. **M. Medley:** None. **N. Dzubuk Pettersson:** None. **J. McCall:** None. **E. Somasundaram:** None. **C. Malloy:** None. **R. Cooper:** None.

**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 471.10/G1

**Topic:** B.08. Synaptic Plasticity

**Support:** DFG Priority Program 1608 Fr1784/17-1

DFG Priority Program 1608 Fr1784/18-1

**Title:** Rebound effect: a late onset replenishment mechanism at a fast auditory synapse

**Authors: *E. G. KRÄCHAN**, T. SCHMITT, M. FUHR, I. RÖMER, V. AUGUSTIN, E. FRIAUF
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**Abstract:** Sound source localization in the mammalian auditory brainstem is achieved by processing interaural time and level differences (ILD). Synapses involved in these tasks are capable of transmitting signals in a precise and reliable manner, even during sustained high-frequency activity. They are equipped with several morphological and molecular features, e.g. inner hair cell ribbon synapses and endbulbs and calyces of Held. The lateral superior olive (LSO) is in the center of the ILD pathway and integrates excitatory signals from the ipsilateral path and inhibitory signals from the contralateral path. Although LSO inputs lack any morphological specifications, they process binaural signals in the millisecond range over sustained periods of time. Here, we assessed the synaptic response characteristics of both inhibitory, glycinergic and excitatory, glutamatergic LSO inputs to continuous (60 s) high-frequency activity (50-200 Hz). In comparison, we inserted 200 ms gaps of silence, a more physiological pattern. We performed whole-cell voltage clamp recordings at LSO neurons of juvenile (P10) and young adult (P35) mice while electrically stimulating excitatory glutamatergic inputs from the cochlear nucleus or inhibitory inputs from the medial nucleus of the trapezoid body (MNTB-LSO). Postsynaptic currents of both LSO inputs showed a frequency-dependent depression. Gaps reduced synaptic depression via replenishment of synaptic vesicles within gaps. As readout of the within-gap replenishment, we analyzed the first ePSC of each burst ($ePSC_1$) and found an unexpected increase of amplitudes after initial short-term depression (STD), which we call rebound effect. The rebound effect was present only at MNTB-LSO synapses and at frequencies >50 Hz. $ePSC_1$ amplitudes increased gradually while the subsequent ePSPCs became reciprocally smaller. The rebound began very late (~20 s), reaching a maximum that was ~25 % higher than the maximal STD levels earlier in the stimulation train. The rebound effect occurred throughout the period analyzed. It is of presynaptic origin because the quantal size was constant during the 60-s trains, which excludes postsynaptic receptor desensitization and saturation. The rebound effect strongly depended on $[Ca^{2+}]_i$ as evidenced by a shift in the onset time after lowering $[Ca^{2+}]_o$ and a strong temporal correlation with asynchronous release. The $Ca^{2+}$ buffer EGTA completely inhibited the rebound. Taken together, we found a novel replenishment mechanism, the rebound effect, at inhibitory MNTB-LSO synapses. It converts tonic responses to onset responses and may thus enable efficient computation of repetitively offered tone bursts.

**Disclosures: E.G. Krächan:** None. **T. Schmitt:** None. **M. Fuhr:** None. **I. Römer:** None. **V. Augustin:** None. **E. Friauf:** None.

**Poster**

**471. Short-Term Plasticity**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 471.11/G2

**Topic:** B.08. Synaptic Plasticity

**Support:** NIH 5R01GM105696

T32 training grant

NW Mitochondrial Research Guild

**Title:** Isoflurane inhibits excitatory synaptic transmission

**Authors: *P. I. ZIMIN**[1,2], C. B. WOODS[1], J. RAMIREZ[3,1], P. G. MORGAN[2,1], M. M. SEDENSKY[2,1]
[1]Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA; [2]Dept. of Anesthesiol. and Pain Med., Univ. of Washington, Seattle, WA; [3]Neurolog. Surgery, Univ. Washington, Seattle, WA

**Abstract:** Mitochondrial complex I dysfunction is linked to volatile anesthetic sensitivity in nematodes, mice and children. Mice with loss of a mitochondrial complex I subunit, NDUFS4, are very hypersensitive to volatile anesthetics (VAs). Limiting NDUFS4 loss to a subset of glutamatergic neurons recapitulated the total knock-out (KO) VA hypersensitivity phenotype. Exposure to 245 µM isoflurane, which anesthetizes KOs but not controls, selectively depressed spontaneous excitatory neurotransmission in KO CA1 neurons. Here we investigated excitatory neurotransmission under conditions of high energetic demand caused by high frequency stimulation (HFS). Evoked field excitatory postsynaptic potentials (fEPSPs) were recorded from CA1 of coronal mouse brain slices. Fibers were stimulated every 30s for baseline activity and for 60min following HFS (3 trains, 100Hz, 20s between trains). In some experiments isoflurane-containing solution was superfused for 40min prior to HFS, and for the duration of the experiment. HFS-induced potentiation in KO slices within 2min post-HFS was ~120%, while control slices showed potentiation to ~160%. By 10min post-HFS, KO and control slopes of fEPSPs displayed very similar potentiation, of ~150%, which gradually decreased to ~120% at 60min. There were no differences between KO and control in the fEPSPs during HFS in the absence of isoflurane. 245 µM isoflurane exposure initially decreased slopes of fEPSPs in the KO to 40% of baseline, gradually increasing to match potentiation in control slices of about 120% over 20min. In 245 µM isoflurane the KO slices displayed much lower slopes in the first 50msec in the second and third train of HFS. 245 µM isoflurane corresponds to ~1.5 isoflurane $EC_{50}$ for the KO. We tested 1.5 isoflurane $EC_{50}$ (735 µM) in controls. Isoflurane reduced fEPSPs to ~25% of baseline at 30s post-HFS, recovering to ~80% by 15min, without further changes.

Application of an $A_1$ adenosine receptor selective antagonist partially eliminated short-term depression in control and KO slices at isoflurane concentrations corresponding to 1.5 times their respective anesthetizing concentrations. Under energetically demanding conditions, isoflurane markedly inhibited the ability of a mitochondrial mutant to recover excitatory synaptic transmission. Depression of mitochondrial function by isoflurane may limit effective neurotransmission in key circuits responsible for responses to VAs in both controls and mitochondrial mutants. Our data are consistent with VAs acting directly within mitochondria to inhibit energy production and depress excitatory transmission, most likely via inhibition of synaptic vesicle recycling.

**Disclosures: P.I. Zimin:** None. **C.B. Woods:** None. **J. Ramirez:** None. **P.G. Morgan:** None. **M.M. Sedensky:** None.

**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 471.12/G3

**Topic:** B.08. Synaptic Plasticity

**Support:** CIHR MOP-81142

NSERC

NIH P41 GM103313

**Title:** Action potential counting at giant mossy fiber synapses gates information transfer in the hippocampus

**Authors: *S. CHAMBERLAND**[1], Y. TIMOFEEVA[2], A. EVSTRATOVA[1], K. E. VOLYNSKI[3], K. TOTH[1]
[1]Cell. and Mol. Neurosci., CRULRG, Quebec, QC, Canada; [2]Univ. of Warwick, Coventry, United Kingdom; [3]UCL Inst. of Neurol., London, United Kingdom

**Abstract:** Neurons encode information in the number and frequency of action potentials they discharge. Presynaptic terminals are key elements involved in the translation of electrical signals to neurotransmitter release. However, how presynaptic terminals decode the frequency and the number of action potentials in incoming bursts through specialized calcium dynamics remains generally unknown.
To investigate how presynaptic terminals translate bursts of action potentials to generate neurotransmitter release, we combined electrophysiological measurements and high resolution presynaptic calcium imaging together with experimentally-constrained modelling of presynaptic calcium dynamics and neurotransmitter release.

We found that action potential transmission from giant mossy fiber terminals to CA3 pyramidal cells was dependent on the number of action potential in the burst, but was independent of the action potential burst average frequency. Consequently, mossy fiber terminals count the number of action potentials in bursts. This information transfer strategy relied on the amount of glutamate released from the presynaptic terminal. These experimental results could be replicated using an experimentally-constrained model of neurotransmitter release, which further revealed that action potential counting can be explained by a unique combination of structural and functional properties of mossy fibre boutons including (i) loose coupling between synaptic vesicles and voltage gated calcium channels, (ii) combined action of fast (calmodulin) and slow (calbindinD28K) endogenous calcium buffers, (iii) slow calcium removal rates and (iv) faster vesicle depletion and higher frequencies. Presynaptic calcium imaging revealed a linear summation of calcium transients during trains of action potentials at 20 Hz and 100 Hz. Our experimental and modelling results indicate that whilst synchronous glutamate release correlates with the peak calcium amplitude within local calcium microdomain at the active zone, asynchronous release depends on the global level of residual calcium in the presynaptic terminal as measured using two-photon calcium imaging.
Thus, our results argue that giant mossy fiber terminals favor a counting logic over rate or temporal coding. Such action potential counting occurs through a unique interplay between short-term facilitation through endogenous calcium buffer saturation and active replenishment of release ready vesicles.

**Disclosures:** **S. Chamberland:** None. **Y. Timofeeva:** None. **A. Evstratova:** None. **K.E. Volynski:** None. **K. Toth:** None.

**Poster**

**471. Short-Term Plasticity**

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**Program#/Poster#:** 471.13/G4

**Topic:** B.08. Synaptic Plasticity

**Support:** KAKENHI 15K00413

KAKENHI 16K00380

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HSR Grants H27-Kagaku-007, MHLW

**Title:** Voltage-sensitive dye imaging study of the input-dependent GABAergic control of the paired burst facilitation (PBF) in area CA1 of the hippocampus

**Authors: *T. TOMINAGA**, Y. TOMINAGA
Inst. of Neuroscience, Tokushima Bunri Univ., Sanuki, KAGAWA, Japan

**Abstract:** The hippocampal system uses several types of oscillatory activities. Input-specific control of the neural activities with such oscillations must make these activities meaningful in the brain. A theta burst stimulation (TBS, a train of brief 100 Hz burst stimulations repeated in 5-7 Hz) that mimics theta oscillation in the rodent hippocampal system is known to induce long-term potentiation (LTP) at area CA1 Schaffer(Sch)-pyramidale synapses. We reported that the TBS caused exaggerated action potential firing during the sequence even in the form of the pair of the brief burst stimulation [PBS; a 100 Hz burst stimulation consists of four stimuli with a 10 ms interval (a priming burst) that precedes a 170 ms interburst interval in the same 100 Hz burst stimulation (a test burst)]. A PBS applied to the Sch induced a facilitated response upon a test burst (a paired burst facilitation; PBF). The PBF can be characterized as follows: the PBF is the membrane potential events in the membrane current. The PBF accompanied the action potentiation of the E-S (EPSP-spike firing) coupling without accompanying an increase of the excitability of the postsynaptic cells while their excitability did not show any increase. Application of Gabazine (SR-95531; GABA-A receptor antagonist) abolished the short-term plastic change of the CA1 circuit caused by PBS. Hence, we hypothesized that PBF has short-term plasticity depending on the neural circuit composed of the principal neuron and interneuron(s). In the CA1 neural circuit, the GABA-A receptor acts either as a feedforward and feedback inhibition. We found that the feedforward inhibition controls the action potential firing of CA1 pyramidal cells. Since the PBF was apparent in the sub-threshold (no action potential) stimulation, we thought that the feedforward inhibition should control the PBF. To examine this possibility, we divided Schaffer collateral fibers into two groups with micro-surgery and applied stimulation into these two separate input pathways. We examined if the burst stimulation to one pathway could induce PBF in the other pathway. The PBF appeared when we delivered a burst stimulation into the same pathway. The PBF may act to control the input pathway's specific amplification for particular oscillatory activity through the network driven neural mechanisms.

**Disclosures: T. Tominaga:** None. **Y. Tominaga:** None.

**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 471.14/G5

**Topic:** B.08. Synaptic Plasticity

**Title:** Bidirectional role of postsynaptic cAMP and cGMP in synaptic plasticity and memory

**Authors: *J. BOROVAC**[1], T. LUYBEN[2], K. TAKAO[3], K. OKAMOTO[4]
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Canada; [3]Life Sci. Res. Ctr., Univ. of Toyama, Toyama-Shi, Japan; [4]Samuel Lunenfeld research institute, Toronto, ON, Canada

**Abstract:** Activity-dependent structural and functional modulation of the synapse are tightly correlated and play an essential role in synaptic plasticity and learning/memory. Postsynaptic cAMP and GMP signaling are crucial for synaptic function, however, the role of cAMP/cGMP in structural change of the synapse remains elusive. Here, we report the role of cAMP/cGMP in bidirectional structural plasticity through interaction with their signal pathways, as well as its role in functional plasticity and related learning/memory.
Strong synaptic activation induces synapse structural enlargement called structural long-term potentiation (sLTP), reorganizing synaptic function through structural change. Using a two-photon optogenetic approach to non-invasively activate light-sensitive adenylyl cyclases at target dendritic spines in the rodent hippocampal CA1 pyramidal neurons, we showed a rapid mechanism of postsynaptic cAMP that enhances sLTP. The cAMP/PKA signal was necessary within 1 min of sLTP induction, independent of cAMP-mediated protein synthesis, and coupled with CaMKIIβ activity which controls the actin cytoskeleton in the spine structure.
In contrast, postsynaptic cGMP was involved in the depotentiation mechanism of cAMP-dependent sLTP. Pharmacological inhibition of cGMP/PKG pathway blocked the depotentiation of cAMP-dependent sLTP, suggesting a crucial inhibitory role of cGMP in cAMP-dependent sLTP. Furthermore, we found postsynaptic cGMP production using a light-sensitive guanylyl cyclase was sufficient to block the cAMP effect of structural potentiation, but not induction of sLTP. These results suggest a bidirectional regulation mechanism of structural potentiation of dendritic spines by postsynaptic cAMP and cGMP signaling pathways.
We have shown that an activity-dependent interaction of CaMKIIβ with actin is critical for controlling not only structural potentiation, but also functional LTP, which implies a tight regulation mechanism between structural and functional plasticity. By establishing the optogenetic manipulation of cAMP/cGMP at target hippocampal neurons in the living mouse brain, we will discuss novel interactive roles of cAMP/cGMP in the hippocampal synaptic potentiation and the related learning/memory.

**Disclosures:** **J. Borovac:** None. **T. Luyben:** None. **K. Takao:** None. **K. Okamoto:** None.

**Poster**

**471. Short-Term Plasticity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 471.15/G6

**Topic:** B.08. Synaptic Plasticity

**Title:** Effects of adenosine on parameters of short-term plasticity in mouse anterior piriform cortex

**Authors: *L. G. NOWAK**[1], S. PERRIER[2], M. GLEIZES[2], C. FONTA[2]
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**Abstract:** Neuronal activity in the brain is characterized by a diversity of oscillatory phenomena, some associated with the sleep/waking cycle and others with diverse behavioral and cognitive processes. Single-unit activity is often linked to the oscillatory activity recorded in the Local Field Potential. The first aim of our study was to determine whether and how different oscillatory activities affect short-term plasticity. For this purpose we used the olfactory system as a model. Indeed, during odorant stimulation, the olfactory bulb displays prominent beta and gamma oscillations. Furthermore, studies showed that the firing of mitral and tufted cells, which project to the anterior piriform cortex, is phase-locked with both beta and gamma oscillations. We examined short-term plasticity in slices of adult mouse piriform cortex maintained *in vitro* in an *in vivo*-like ACSF. In our *in vitro* study, we replaced the presynaptic neuronal firing rate by controlled and repeated electrical stimulation (trains consisting in 5 pulses, frequency between 3.125 and 100 Hz) applied to the lateral olfactory tract. Postsynaptic responses were recorded in layer 1a of the piriform cortex. Our results revealed a considerable enhancement of postsynaptic response amplitude for stimulation frequencies in the beta and gamma range. The data were fit with a phenomenological model of short-term plasticity adapted from that of Tsodyks et al. (1997). The parameters of the model indicate that the observed results can be explained by the interplay between a short-term facilitation mechanism (time constant 160 msec) and two short-term depression mechanisms, with fast (less than 20 msec on average) and slow (140 msec) recovery time constants. The second aim of our study was to examine the effect of adenosine on short-term plasticity. Indeed, at the cortical level adenosine plays a prominent role in synaptic transmission as a presynaptic inhibitory neuromodulator. In the presence of adenosine (10-1000 µM), response amplitude decreased while short-term plasticity became more dominated by facilitation. Hence facilitation compensated for decreased response amplitude in a frequency dependent manner: compensation was strongest at high frequency, up to restoring response amplitude to that measured in control conditions. The model suggested that the principal effect of adenosine was to decrease initial release probability; increased facilitation hereby ensued due to increased available resources. Altogether these results suggest that adenosine acts as a high-pass filter.

**Disclosures: L.G. Nowak:** None. **S. Perrier:** None. **M. Gleizes:** None. **C. Fonta:** None.

**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.01/G7

**Topic:** B.08. Synaptic Plasticity

**Support:** R01 MH101528-01

NSF GRFP

**Title:** Distinct neuronal activity patterns induce different gene expression programs

**Authors: *K. TYSSOWSKI**[1], N. DESTEFINO[1], R. N. SAHA[2], J.-H. CHO[1], R. JONES[1], S. CHANG[1], P. ROMEO[3], M. WURZELMANN[3], J. WARD[3], S. M. DUDEK[3], J. GRAY[1]
[1]Harvard Med. Sch., Boston, MA; [2]Univ. of California Merced, Merced, CA; [3]Neurobio. Lab., Natl. Inst. of Env. Hlth. Sci., NIH, Research Triangle Park, NC

**Abstract:** Brief and sustained neuronal activity patterns can have opposite effects on synaptic strength that both require activity-regulated gene (ARG) expression. However, whether distinct patterns of activity induce different sets of ARGs is unknown. In genome-scale experiments, we reveal that a neuron's activity-pattern history can be predicted from the ARGs it expresses. Surprisingly, brief activity selectively induces a small subset of the ARG program that that corresponds precisely to the first of three temporal waves of genes induced by sustained activity. These first-wave genes are distinguished by an open chromatin state, proximity to rapidly activated enhancers, and a requirement for MAPK/ERK signaling for their induction. MAPK/ERK mediates rapid RNA polymerase recruitment to promoters, as well as enhancer RNA induction but not histone acetylation at enhancers. Thus, the same mechanisms that establish the multi-wave temporal structure of ARG induction also enable different sets of genes to be induced by distinct activity patterns.

**Disclosures: K. Tyssowski:** None. **N. DeStefino:** None. **R.N. Saha:** None. **J. Cho:** None. **R. Jones:** None. **S. Chang:** None. **P. Romeo:** None. **M. Wurzelmann:** None. **J. Ward:** None. **S.M. Dudek:** None. **J. Gray:** None.

**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.02/G8

**Topic:** B.08. Synaptic Plasticity

**Support:** CDMRP Grant W81XWH-08-2-0136 to MJF

**Title:** The effects of neural stimulation pattern on gene expression in the cerebral cortex

**Authors: *M. M. CHAUDHRY**[1], Q. S. FISCHER[2], H. KALIKULOV[2], M. J. FRIEDLANDER[2]
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**Abstract:** Empirical evidence from deep brain stimulation studies has shown that a variety of different parameters, including stimulation frequency and pattern influence the efficacy of the procedure. However, there is little information available regarding the long-term downstream changes evoked by such stimulation including changes in gene expression. We asked whether the temporal pattern of synaptic conditioning influences the expression of specific genes.
Acute occipital cortical slices were prepared from 10-12 week old rats, slices were cut at 300 μm and bathed in aCSF (124 NaCl, 2 KCl, 0.2 $CaCl_2$, 3.5 $MgCl_2$, 26 $NaHCO_3$, 10 D-glucose, and saturated with a 95% $O_2$-5% $CO_2$). Slices were perfused in a chamber with aCSF at 32-35 C°. A stimulating rake-electrode was positioned in the fourth layer of the primary visual cortex with a field potential (FP) recording electrode placed in layer 2/3. The slices were treated with one of four conditions: a 15 minute discontinuous (groups of stimuli separated by equal rest periods) conditioning train at 10 Hz with regular inter-stimulus intervals, a 15 minute discontinuous conditioning train at 10 Hz with stimuli having a highly irregular distribution of interstimulus intervals (Poisson distributed), a 15 minute continuous conditioning train at 100 Hz with regular inter stimulus intervals, or no stimulation (control). In all conditions, there was a 15-minute pre and post-conditioning period with stimulation at 0.1 Hz to evoke FPs. Each group was divided according to plasticity outcome (LTP -Long Term Potentiation, LTD -Long Term Depression or no change).Three hours after the conditioning, layer 2/3 above the stimulation electrode was dissected in aCSF. RNA was extracted using Bio-Rad Aurum Total RNA kit**.** Samples were processed with RNAseq. Sequences were aligned via Tophat2 and counted via HTSeq. mRNA differential expressions were tested for significance using the Benjamini-Hochberg corrected Wald Test in DESeq2. The main effect of stimulation pattern was found between the control (no stimulation) group and the group that experienced 100 Hz regular conditioning where LTD was induced by the conditioning. In those cases, six genes had significant differential expression. Fbxw7 was upregulated by 1.35 fold, Ddx10 was upregulated by 1.41 fold, Mkx was upregulated by 1.49 fold, Cass4 was upregulated by 1.51 fold, Nyap2 was upregulated by 1.50 fold, Adamsts12 was down regulated by 0.63 fold, and Fbn2 was upregulated by 1.49 fold in the 100 Hz regular LTD vs. control group. No other significant differences were found between any of the other groups. These results are considered in the context of these genes and long term synaptic plasticity.

**Disclosures: M.M. Chaudhry:** None. **Q.S. Fischer:** None. **H. Kalikulov:** None. **M.J. Friedlander:** None.

**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.03/G9

**Topic:** B.08. Synaptic Plasticity

**Support:** DHHS/NIH/NIDA/IRP

**Title:** Compulsive methamphetamine taking under punishment increases the expression of AP1 family of transcription factors in the rat nucleus accumbens

**Authors: *M. T. MCCOY**, B. LADENHEIM, L. CONTU, M. O. JOB, B. CAMPBELL, C. A. BLACKWOOD, S. JAYANTHI, J. CADET
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**Abstract:** Methamphetamine is an illicit psychostimulant that is abused worldwide. Its continuous use is accompanied by many medical, neurological, and psychiatric complications. So far, however, there is no pharmacological treatment that has proven to be beneficial to this patient population. This lack of comprehensive pharmacological approaches may be related to the insufficient understanding of cellular and molecular mechanisms of methamphetamine addiction. As a first step towards identifying the molecular bases of compulsive methamphetamine taking, our laboratory has started to use footshocks as adverse consequences during methamphetamine self-administration (SA) because the definition of addiction includes the presence of negative outcomes. We use that model to measure potential changes in the expression of immediate early genes (IEGs) in the nucleus accumbens of rats during early withdrawal times from methamphetamine SA. Male Sprague-Dawley rats were trained to self-administer METH (0.1 mg/kg/injection, i.v.) or saline during twenty-one (9-hr daily access) sessions. After that time, foot-shocks were administered in increasing intensity over a period of eight sessions. We included additional control groups that were yoked for non-contingent footshocks to the rats that received methamphetamine and contingent foot-shocks. Foot-shocks caused the separation into two distinct methamphetamine SA groups: (1) shock-resistant (SR) rats that continued to press the lever for methamphetamine despite punishment and (2) shock-sensitive (SS) rats that significantly reduced their lever pressing. The rats were euthanized 2h after the last session. We then extracted RNA from the NAc, made cDNA, and ran quantitative polymerase chain reaction (PCR) to measure the expression of several IEGs including cfos, fosB, Fra1, and Fra2. We also measure the expression of cjun, junB, and junD mRNAs. SR rats showed significant increases in cfos, fosB, Fra2, and junB mRNA levels in the nucleus accumbens. Animals yoked to the SR rats showed no changes in the expression of these IEGs, indicating that these effects are specific to compulsive methamphetamine taking. These observations indicate that compulsive methamphetamine taking may be initiated activation of complex downstream targets of these IEGs. This model of self-administration associated with adverse consequences may provide greater insight into the neurobiology of methamphetamine addiction.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.04/G10

**Topic:** B.08. Synaptic Plasticity

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**Title:** Role of the transcription factor Nurr1 on glutamatergic synapses in the hippocampus

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**Abstract:** Long-term potentiation (LTP) and long-term depression (LTD) are cellular events widely believed to underlie learning and memory. Regulation of the AMPA-type ionotropic glutamate receptor (AMPAR) levels at the synapse is crucial to postsynaptic forms of LTP and LTD of excitatory transmission. Several factors, including neurotrophins, modulate exo- and endocytosis of synaptic AMPARs, and also participate in the regulation of their gene expression. We have previously reported that the neurotrophin BDNF is a target gene of the nuclear receptor related protein 1, Nurr1, an orphan nuclear transcription factor. However, the potential role of Nurr1 on AMPAR-mediated synaptic function remains unknown. In this study, we tested whether Nurr1 transcriptional activity participates in the activity-dependent modulation of AMPARs in cultured hippocampal neurons and acute hippocampal slices. We found that Nurr1 expression is low in basal conditions, but it increases upon synaptic stimulation in mature hippocampal neurons. This increase is dependent on calcium entry through ionotropic glutamate receptors and requires the activation of the CREB-CRTC1 signaling pathway and calcineurin. In addition, Nurr1 agonists increased both BDNF and the GluA1 subunit levels in cultures, and

partially blocked LTD at CA3-CA1 synapses in hippocampal slices, suggesting that Nurr1 is involved in the activity-dependent modulation of BDNF and AMPAR-GluA1 subunit. Together, our findings indicate that Nurr1 could play a role in AMPAR plasticity associated to learning and memory events.

**Disclosures:** **J. Català-Solsona:** None. **D.J. Siedlecki-Wullich:** None. **S. Lutzu:** None. **P.J. Lituma:** None. **C. Fábregas-Ordoñez:** None. **C.A. Saura:** None. **A.J. Miñano-Molina:** None. **P.E. Castillo:** None. **J. Rodríguez-Álvarez:** None.

**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** B.08. Synaptic Plasticity

**Support:** Lieber Institute

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NIMH R01MH1055929

**Title:** Impact of BDNF signaling on maternal care and oxytocin neuron gene expression

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**Abstract:** Oxytocin (OXT) is a neuropeptide critical for regulation of social behaviors. Brain-derived neurotrophic factor (BDNF) and its receptor TrkB are highly expressed in the paraventricular hypothalamus, a key site of neuroendocrine cells secreting OXT. Transcription of *Bdnf* is controlled by several promoters, which drive expression of multiple transcripts encoding an identical protein. *Bdnf* promoter I significantly contributes to BDNF production in the hypothalamus. Female mice with selective disruption of promoter I-derived BDNF (Bdnf-e1 -/-) show impaired maternal care, reduced *Oxt* transcripts, and enhanced aggression towards foreign pups. To better understand the role of BDNF signaling in OXT neuron function, we used TRAP (translating ribosome affinity purification) and RNA sequencing (RNAseq) to examine cell-type-specific gene expression in OXT neurons from wild-type and Bdnf-e1-/- females. First, to validate our technique and identify transcripts enriched in OXT neurons, we crossed mice expressing Cre recombinase under control of the endogenous *Oxt* promoter to the RiboTag

mouse, which expresses a hemagglutinin (HA) tag on the ribosomal protein RPL22 under control of Cre. Ribosome-associated mRNAs were affinity purified with a HA antibody and characterized using high-throughput RNAseq analysis. To elucidate changes in OXT gene expression following perturbations in BDNF signaling, we used an adeno-associated viral (AAV) Ribotag approach to isolate and sequence ribosome-associated transcripts in OXT neurons from control and Bdnf-e1 -/- females with impaired maternal care. Here we report genes and gene pathways highly enriched in OXT neurons and provide a molecular profile defining the OXT neuron transcriptome. We also identify transcripts vulnerable to misregulation in OXT neurons following loss of hypothalamic BDNF signaling. These results demonstrate the molecular dissection of a sexually dimorphic hypothalamic population that governs complex social behaviors. Our findings also identify BDNF-dependent signaling pathways in OXT neurons that can be targeted to modulate social function.

**Disclosures: K.R. Maynard:** None. **J. Hobbs:** None. **B. Phan:** None. **C. Williams:** None. **A. Gupta:** None. **J. Shin:** None. **A. Jaffe:** None. **K. Martinowich:** None.

**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

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**Topic:** B.08. Synaptic Plasticity

**Support:** NIH Grant R01MH097803

**Title:** Induction of BDNF by Electroconvulsive stimulation requires the immediate early gene early growth response 3 (Egr3)

**Authors: *K. MEYERS**[1], K. K. MARBALLI[2], J. M. CAMPBELL[1], A. L. GALLITANO[3]
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**Abstract:** Electroconvulsive therapy (ECT) is one of the most effective treatments for severe psychotic and mood disorders. ECT is rapid and safe, and is used as a first-line treatment for medication resistant illnesses such as psychotic depression. However, the mechanisms underlying the therapeutic efficacy of ECT remain unknown. One candidate for an important role in ECT is brain derived neurotrophic factor (BDNF), which is activated by electroconvulsive seizure (ECS). Disruption of hippocampal BDNF attenuates the effect of antidepressants, and infusion of BDNF into the hippocampus reverses depression-like behavior in rodents. But the mechanism by which neuronal activity regulates *Bdnf* expression is unclear. We hypothesized that immediate early genes, which are rapidly activated at high levels in the brain in response to ECS, may regulate neurotrophic factors, including *Bdnf*. To test this hypothesis, we conducted an

expression microarray on RNA isolated from hippocampal tissue from wildtype and *Egr3* deficient (*Egr3*-/-) male mice one hour post ECS (versus no-ECS, baseline control). Experimental results identified *Bdnf* as one of 63 differentially expressed genes in WT compared with *Egr3*-/- mice following ECS. This result was validated by quantitative RT-PCR in the RNAs used for the microarray, as well as in two independent cohorts of female *Egr3*-/- and matched WT littermate mice. *In situ* hybridization showed that ECS induced high level expression of *Bdnf* mRNA in the hippocampal dentate gyrus of WT mice one hour post ECS, with cellular distribution in the Cornu Ammonis 3 region (CA3). In contrast, no increase in *Bdnf* expression was seen in *Egr3*-/- mice. These findings support the hypothesis that *Egr3* may be required for activation, or maintenance, of *Bdnf* expression in the hippocampus in response to acute ECS. These findings suggest that the immediate early gene transcription factor *Egr3* may play an essential role in translating neuronal activity into the molecular changes that underlie the therapeutic effect of ECT.
*Authors contributed equally.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

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**Topic:** B.08. Synaptic Plasticity

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**Title:** Early growth response 3 (Egr3) is a novel regulator of DNA damage response genes in the mouse hippocampus

**Authors: *K. MARBALLI**[1], S. BRUNWASSER[1], K. MEYERS[1,2], A. BARKATULLAH[1], J. CAMPBELL[1], A. L. GALLITANO[1]
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**Abstract:** Early growth response (Egr) immediate early gene (IEG) transcription factors are crucial regulators of synaptic plasticity and are critical for memory formation. Egr family members *EGR1* and *EGR3* are associated with risk for psychiatric illnesses, including schizophrenia, and are reduced in the brains of these patients. Psychiatric disorders are accompanied by cognitive and memory deficits. In addition, brain tissue from psychiatric disorder patients show high levels of DNA damage. Recent studies have found that DNA damage induced by normal physiologic activity induces expression of IEGs such as *Egr1* in

neurons. These studies suggest that DNA double strand breaks, a form of DNA damage may serve as an “on” switch for activation of IEGs which, in turn, regulate synaptic plasticity and memory formation. However, for IEGs to be ready to respond to a subsequent stimulus, this damage must be repaired. Here we report that *Egr3* regulates genes involved in DNA repair in response to neuronal activity. In order to identify novel gene targets of EGR3 in the hippocampus, we carried out global gene expression studies using a microarray in both wild type (WT) and *Egr3-/-* male mice using a model of *Egr3* induction namely electroconvulsive seizure (ECS). Briefly male mice received no ECS/ ECS (n = 4 per group) followed by hippocampal RNA extraction and global gene expression analyses carried out using Illumina WG-6 microarray. Gene pattern and Genome studio programs were used for identifying differentially expressed genes (DEGs). Validation of candidate genes was carried out using quantitative real time PCR in both the original male cohort and an independent female cohort (n = 4-5 per group). 64 common genes identified in both programs were used for biological and functional analysis using Ingenuity pathway analysis (IPA). GADD45B (growth arrest and DNA-damage-inducible 45 beta) signaling (p = 2.04 E-05) was revealed as the top pathway in WT mice vs. *Egr3-/-* 1 hour post-ECS. A literature survey revealed at least 13 genes from the differentially expressed gene list to be involved in DNA damage response. We successfully validated 7 of these genes in the original male cohort and 3 genes in both the original male and an independent female cohort. Based on these results we hypothesize that *Egr3* regulates genes that repair or “turn off” the DNA damage “switch” that activates IEGs. Dysfunction in *Egr3* may thereby result in an accumulation of DNA damage contributing to cognitive and neurobehavioral deficits.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

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**Topic:** B.08. Synaptic Plasticity

**Support:** NIH

NSF

**Title:** Genomic identity and plasticity of cAMP-dependent genes in *Aplysia* californica

**Authors: *C. BOSTWICK**, T. P. MOROZ, A. B. KOHN, L. L. MOROZ
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**Abstract:** The second-messenger intracellular signaling molecule cyclic adenosine monophosphate (cAMP) orchestrates a myriad of cellular processes, including long-term synaptic plasticity and memory, through its effects on the cAMP-dependent protein kinase (PKA). Several proteins and molecules involved in the initial cAMP-dependent signaling cascade have been elucidated, but less is known of the molecules “downstream” of the signaling cascade, particularly those that are recruited and activated several hours after signaling initiation. In order to gain a more comprehensive understanding of the cAMP/PKA molecular pathway, we utilized next-generation high-throughput sequencing to query the nervous cells of a classic neuroscience model, the sea hare *Aplysia californica.* We divided the Aplysia central nervous system (CNS) into individual ganglia and treated those ganglia with a cAMP-derivative (8-bromo-cAMP) for various lengths of time to activate the cellular cAMP/PKA signaling pathway. This allowed us to identify cAMP/PKA-dependent genes that are differentially expressed between the various ganglia subtypes of the Aplysia CNS as well as differential expression of cAMP/PKA-dependent genes in the same ganglia over the course of 8-bromo-cAMP treatment. We discovered hundreds of differentially expressed transcripts. These transcripts encode chromatin-remodeling enzymes, ion channels, cellular receptors, transcription factors, and regulatory kinases or phosphatases, among others. Some of the differentially expressed transcripts are “uncharacterized”, meaning their function or cellular role is currently unknown, and potentially unique to Aplysia. Among the incredible assortment of roles these uncharacterized transcripts may play are the regulation of gene expression, facilitation of protein-protein interactions, involvement in novel cell signaling, or the modification of cellular RNA after transcription. In addition to uncharacterized transcripts, we identified differentially expressed neuronal-specific long noncoding RNAs (lncRNA) that may potentially mediate previously unidentified regulatory roles within the nervous system. This comprehensive study of the genetic identity of molecules and cellular processes involved in the cAMP-dependent signaling cascade over time and across the Aplysia CNS can provide a foundation to understanding the dynamics of this crucial and ubiquitous cellular signaling pathway and its effects on long-term synaptic plasticity and memory.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

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**Topic:** B.08. Synaptic Plasticity

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**Title:** CoREST expression in the pilocarpine-induced status epilepticus in mice

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**Abstract:** CoREST (CoREST1, rcor1) is member of a family of transcriptional corepressors that also comprise CoREST2 (rcor2) and CoREST3 (rcor3). CoRESTs form complexes (LCH) with the histone demethylase LSD1 and deacetylases HDAC1 and HDAC2 to epigenetically modify chromatin packaging. Previously, we have shown that LCH complexes formed by the different CoREST display differential capabilities. Indeed, CoREST2 have less repression capacity and lower interaction with HDAC1/2, suggesting that CoREST2-containing LCH complexes play different functional role than CoREST1-containing LCH complexes. Several lines of evidence show that the expression of proteins forming LCH complexes is regulated by neuronal hyperexcitability. For instance, HDAC2 increases during temporal lobe epilepsy and the expression of the neuronal splice variant of LSD1 increases in the hippocampus of mice with pilocarpine-induced seizures. Since CoRESTs are platform proteins bringing HDAC1/2 and LSD1 to chromatin, we hypothesized that their expression is also regulated during hyperexcitability. To this end, we treated mice with the muscarinic cholinergic agonist pilocarpine to induce seizures in the temporal lobe of the brain. Using this model, we replicated previous data showing that the ratio between neuroLSD1 and LSD1 increases while total protein levels do not change in the hippocampus after 24 hours of seizure. Under the same conditions, CoREST1 and CoREST2 mRNA expression and proteins levels are modified in the mice hippocampus. The data were also replicated in hippocampal neurons in culture and hippocampal cell lines treated with pilocarpine. Altogether, the data indicate that CoREST1 and CoREST2 expression is regulated by hyperexcitability.

**Disclosures:** **M.E. Andres:** None. **C.A. Rivera:** None. **V. Noches:** None.

**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

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Conicyt PhD Fellowship 21161044

**Title:** Dynamic recruitment of CoREST proteins to neuronal chromatin

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**Abstract:** CoREST1, 2 and 3 proteins belong to a transcriptional co-repressor family that regulates neuronal gene expression in non-neuronal tissues and neural progenitors. These proteins recruit the chromatin modifying enzymes, histone demethylase LSD1 and histone deacetylases HDAC1 and HDAC2 forming the biochemically stable protein complex LCH. The best-characterized protein of this family is CoREST1, which can be recruited to chromatin by binding transcription factors or directly to the nucleosome, where the enzymatic activities of LSD1 and HDAC1/2 are required to repress gene transcription. Previous work of our laboratory has shown that the transcriptional repressor capacity of CoREST proteins is different. In addition, it has been shown that LCH subunits can be post-translationally modified disrupting the complex integrity. Together, these data support the hypothesis that the composition of the complex is post-translationally regulated. In this work, we use biochemical techniques to show that chromatin association of different subunits of the LCH complex is dynamic and can be altered in animal and cellular models of pharmacologically induced neuron hyperexcitability. In basal conditions, we observed that CoREST1 and CoREST2 are distributed in the subcellular fractions corresponding to insoluble chromatin, soluble cytoplasmic and nucleoplasmic fractions. However, CoREST3 is found only as soluble complexes in nucleosome-free fractions, suggesting a differential chromatin affinity for CoREST proteins. To induce hyperexcitability we treated hippocampal cell cultures with pilocarpine, a muscarinic cholinergic agonist, during 24 hrs. CoREST2, HDAC1 and HDAC2 were globally recruited to chromatin in hippocampal cells resulting in the modification of histone lysine acetylation and methylation. Our results indicate that each CoREST protein differentially affect the global chromatin state in terms of post-translational modifications of histones and DNAse accessible regions.

**Disclosures: C.A. Rivera:** None. **V. Noches:** None. **M.E. Andres:** None.

**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

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**Title:** Upf1 contributes to Arc/Arg3.1 gene expression

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**Abstract:** In the mammalian central nervous system, each neuron receivers signals from other neurons synapses located on its cell body and dendrites. The numerous proteins in a cell must be in the right place at the right time to carry out their functions. In a manner unique among activity-regulated immediate early genes (IEGs), mRNA encoded by Arc (also known as Arg3.1) undergoes rapid transport to dendrites and local synaptic translation. From now on, arc mRNA is thought to be a natural target for nonsense-mediated mRNA decay (NMD) by virtue of its two conserved 3′-UTR introns. NMD and other related translation-dependent mRNA decay mechanisms may serve as critical brakes on protein expression that contribute to the fine spatial-temporal control of Arc synthesis. Here in our study, low basal level of Arc gene expression is also regulated by Upf1 in transcriptional- and translational-manner. Furthermore, sustained expression of Arc by reducing of Upf1 contributions to cofilin phosphorylation and abnormal neuronal outgrowth.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** B.08. Synaptic Plasticity

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**Title:** The mRNA methyltransferase METTL14 is vital for survival and epitranscriptomic regulation of learning

**Authors: *J. KORANDA**[1], L. DORE[3], H. SHI[4], M. PATEL[5], L. VAASJO[7], M. RAO[6], W. CHI[1], K. CHEN[6], Z. LU[6], C. HE[6], X. ZHUANG[2]
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**Abstract:** Recent discoveries of reversible mRNA modifications have generated interest in the epitranscritptome. $N^6$methyladenosine ($m^6A$), the most abundant mammalian mRNA modification, affects almost every aspect of mRNA metabolism, including RNA splicing, export, localization, translation efficiency, and stability. Studies in cell lines have demonstrated that $m^6A$ plays a critical role in stem cell differentiation and cellular stress response. Much less is known about the role of $m^6A$ in postmitotic cells such as neurons. Interestingly, $m^6A$ brain levels remain low throughout mouse embryogenesis, but increase dramatically by adulthood. Polymorphisms in FTO (fat mass and obesity-associated protein), an $m^6A$ demethylase, have been linked to obesity, addiction, ADHD, and nucleus accumbens reactivity. Moreover, deletion of FTO increases $m^6A$ levels and alters dopaminergic signaling in mice, and a recent study has shown that fear conditioning can elevate $m^6A$ levels in prefrontal cortex while knockdown of FTO enhances memory consolidation. While these and other studies implicate the importance of $m^6A$ in brain function, no studies exist examining the consequences of $m^6A$ deficiency in animals. To prevent $m^6A$ deposition in neurons, we generated a floxed *Mettl14* allele ($M14^{f/f}$). *Mettl14* encodes an essential component of the $m^6A$ methyltransferase complex. Using the Meox2-cre germline deleter strain, we found that constitutive deletion of *Mettl14* is embryonically lethal. To circumvent this lethality, we crossed $M14^{f/f}$ mice with mice expressing Cre recombinase under direction of the Drd1 promoter (D1Rcre) to selectively delete METTL14 from striatonigral neurons. Striatonigral METTL14 deletion decreased striatal $m^6A$ levels, and transcriptome-wide $m^6A$ profiling and mRNA-seq revealed global changes in mRNA levels in the striatum. A distinct subset of downregulated mRNAs tended to encode neuronal or synaptic proteins, while upregulated mRNAs tended to encode proteins involved in metabolism and translational regulation. Behaviorally, METTL14 deletion in striatonigral neurons altered key functions of these neurons: responses to dopaminergic drugs and motor learning. The functional consequences of $m^6A$ deficiency in postmitotic neurons was further confirmed by viral-mediated neuron specific deletion of METTL13 in the dorsal striatum of adult mice.

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**Poster**

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Max Planck Florida Institute

**Title:** *In vivo* 2pFLIM imaging of experience dependent dynamics of CREB with cellular resolution

**Authors: *T. LAVIV**, P. PARRA-BUENO, R. YASUDA
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**Abstract:** A major quest in neuroscience is to decipher the remarkable dynamics of the structure and function of the brain during experience dependent plasticity. Previous studies using *in vitro* models such as LTP/LTD, have determined in exquisite details the molecular mechanisms of synaptic plasticity. However, very little is known regarding ongoing *in vivo* molecular dynamics in the brain , during learning. This is primarily due to lack of technical approach for monitoring protein dynamics *in vivo*. Furthermore, accumulative evidence have shown a prominent role for transcription and translation of new genes and proteins during learning and memory. However, it was not possible to directly measure the relationship between transcription/translation and neuronal activity. In order to try and bridge this gap, we have established an imaging based approach to enable *in vivo* 2-photon Fluorescence lifetime imaging (FLIM) measurements of protein activity in the mouse cerebral cortex. 2pFLIM is advantageous for chronic *in vivo* imaging since it does not depend on changes in fluorescence intensity, which are prominent during these experiments, and therefore allows chronic reliable measurement of bio-sensor activity in the brain. In order to measure molecular dynamics at the level of single cells, we have established and characterized a FLIM bio-sensor for nuclear CREB activity, a well-known transcription factor which plays a vital role in long term memory and synaptic plasticity. This system allows us to perform chronic FLIM based measurements of CREB activity levels in single cell resolution in cortical layer 2/3 cells. Using this technique we were able to demonstrate a dynamic increase in CREB activity during enriched sensory environment as well as during motor learning. Furthermore, exploiting recently identified RFPs suitable for FLIM, have now allowed us to perform dual-color FLIM using red-shifted biosensors alongside GCaMP6 calcium

sensor, which enables us to measure CREB dynamics along neuronal activity simultaneously in the same population of cells. Therefore, this approach provides direct access to real-time monitoring of protein signaling dynamics and neuronal activity *in vivo*. In the future, this experimental approach could be applied to a wide range of signaling molecules and brain regions, allowing dissection of the temporal dynamics of various signaling proteins in the living brain.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.14/H10

**Topic:** B.08. Synaptic Plasticity

**Support:** This work was supported by the National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, Division of Intramural Clinical and Biological Research (DICBR)

**Title:** Expression of the small G-protein Rem2 is transcriptionally regulated by CREB

**Authors: *H. L. PUHL, III**, D. J. LIPUT, M. D. AKBAR
NIH, Rockville, MD

**Abstract:** Rem2 is a member of the RGK subfamily of the RAS superfamily of small G-proteins. Rem2 has a more neuronal expression pattern compared to other RGK proteins and is expressed in a temporally controlled and very restricted distribution within the central and peripheral nervous systems. Rem2 has been shown to inhibit high voltage activated calcium channels and influence synaptogenesis and dendritic arborization. Aside from the regulation of Rem2 expression by calcium, not much is known about its transcriptional control. To investigate potential transcriptional elements involved in Rem2 expression we first identified several mouse neuroblastoma cell lines including Neuro2A, N1E-115, ND7/23 (rat/mouse fusion) and a pituitary tumor line ATT20 that endogenously express Rem2 mRNA (qPCR) and protein (Western blot). Rem2 expression was not detected in non-neuronal lines such as L cells and NIH3T3. Rem2 expressing cell lines were used in a dual luciferase assay to identify a 3.6 kb region upstream from the 5'UTR of the mouse Rem2 gene with promoter activity. Using a deletion approach, expression peaked with a 600bp fragment which included the 5'UTR, plateaued, and ceased within the 5'UTR, 93bp from the translational start site. Deletion or mutagenesis of several putative transcription factor binding sites (TFBS) for factors such as CREB (CRE), NFkB, Sp1 and ElkI did not alter luciferase expression levels. Surprisingly, cotransfection of a constitutively active CREB fusion protein (VP16-CREB) with the 600bp

promoter fragment reporter resulted in about a 5-fold increase in luciferase activity. This induction was observed in constructs with various TFBS mutations including several predicted CRE sites. Using qPCR, we found transfection of N1E-115 with VP16-CREB mRNA induced a 33-fold increase in Rem2 mRNA, while transfection of ND7/23 with a plasmid encoding VP16-CREB induced a 112-fold increase in Rem2 mRNA. Rem2 has been shown to express well in regions of the basal ganglia such as the striatum. We observed a time dependent increase in Rem2 mRNA measured by qPCR following exposure of primary striatal cultures to the adenylate cyclase activator forskolin. Furthermore, transfection of primary striatal cultures with VP16-CREB mRNA produced a dose dependent increase in Rem2 mRNA expression. Taken together these data suggest the expression of Rem2 is induced by CREB at the transcriptional level in cell lines and neurons. The inability of TFBS mutagenesis to affect this induction in cell lines suggests the CREB effect may be indirect. Finally, Rem2 expressing cell lines identified here will provide a useful tool to further study Rem2 function and expression.

**Disclosures: H.L. Puhl:** None. **D.J. Liput:** None. **M.D. Akbar:** None.

**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

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**Topic:** B.08. Synaptic Plasticity

**Support:** NIH 5R01MH105398

John Templeton Foundation

NHMRC (APP1033127-TWB)

**Title:** Self-Scission of the CPEB3 ribozyme is activity-dependent and may regulate expression of the CPEB3 mRNA

**Authors: *C. CHEN**[1], X. LI[3], K. KE[1], T. W. BREDY[3], A. LUPTÁK[2]
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**Abstract:** Neuroplasticity, a dynamic change in synaptic strength, is pivotal for learning and memory. At the cellular and molecular level, regulation of RNA transcription and *de novo* protein synthesis at synapses have been implicated in long-term synaptic plasticity. Cytoplasmic polyadenylation element-binding protein 3 (CPEB3) is a sequence-specific RNA binding protein that has been shown to regulate polyadenylation-induced mRNA stability in dendrites and thereby mediate synaptic plasticity. Previous studies have demonstrated that a single nucleotide polymorphism (SNP) in the intronic sequence of *CPEB3* is associated with human episodic

memory. Notably, the intronic sequence in which this allele of SNP is located has been identified in a self-cleaving ribozyme. However, how CPEB3 ribozyme affects mRNA expression in neurons remains unexplored. In this study, we investigated the role of CPEB3 ribozyme in regulating its mRNA expression in response to neuronal stimulation. Primary cortical neurons were stimulated by potassium chloride (KCl) or glutamate application, and gene expression of CPEB3 was examined at various time points. CPEB3 mRNA expression was up-regulated at two hours after glutamate stimulation, yet it was down-regulated at prolonged time points, which was correlated with the CPEB3 ribozyme expression. Similarly, membrane depolarization by KCl resulted in an up-regulation of CPEB3 mRNA and ribozyme expression at one hour compared with unstimulated cultures. Repeated KCl-induced depolarization led to a reduction in CPEB3 mRNA expression, whereas, ribozyme expression was elevated. Collectively, those results suggest that the self-cleaving CPEB3 ribozyme might regulate mRNA and protein expression of CPEB3 in neurons, and this activity-dependent induction might contribute to neuroplasticity.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.16/H12

**Topic:** G.07. Other Psychiatric Disorders

**Support:** DP1DA042078

MQ: Transforming Mental Health Research Fellowship; MQ15FIP100011

**Title:** Histone serotonylation: A novel mechanism of epigenetic plasticity

**Authors: *L. FARRELLY**[1], R. THOMPSON[2], S. ZHAO[3], A. E. LEPACK[1], B. J. LUKASAK[2], T. NAKADAI[4], Y.-H. LOH[1], Y. LU[1], R. M. BASTLE[1], O. BERTON[1], H. ZEBROSKI III[4], N. ALENINA[5], M. BADER[5], N. BHANU[6], H. MOLINA[4], B. A. GARCIA[6], R. G. ROEDER[4], L. SHEN[1], H. LI[3], T. W. MUIR[2], I. MAZE[1]
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**Abstract:** Monoamines, such as serotonin, dopamine, etc., play a critical role in neuronal plasticity, with alterations implicated in the development and treatment of numerous brain disorders. Although vesicular packaging of monoamines is essential for neurotransmission, recent data have demonstrated the additional presence of ‘reserve’ pools of extravesicular

monoamines in the nucleus of monoaminergic neurons; it has remained unclear, however, whether nuclear monoamines may play roles independent of neurotransmission. Serotonin has previously been shown to form covalent bonds with certain cytoplasmic proteins via transamidation by the tissue transglutaminase 2 (TGM2) enzyme, a process known as serotonylation. Since this modification alters the signaling properties of its substrates, we hypothesized that nuclear proteins may similarly be modified to control distinct aspects of their function.Here, we describe histone proteins-specifically histone H3 glutamine 5 (H3Q5ser)-as novel substrates for monoaminylation *in vivo* and have delineated, at least in part, the biophysical, biochemical and molecular functions of this novel modification in the context of neuronal development and transcriptional plasticity. Utilizing a unique combination of biochemical, genome-wide and neurobiological approaches, our data indicate that H3 serotonylation acts to facilitate binding of adjacent H3 methylation binding proteins (e.g., pre-initiation complex subunits, such as TAF3/TFIID), thereby promoting neuronal genic activation and the facilitation of neural differentiation. In sum, our data provide the first direct evidence that hydrophobic monoamines in brain contribute directly to neuronal gene expression via a novel, neurotransmission-independent epigenetic mechanism, phenomena that will likely have broad implications within the field of neuroscience and beyond.

**Disclosures:** **L. Farrelly:** None. **R. Thompson:** None. **S. Zhao:** None. **A.E. Lepack:** None. **B.J. Lukasak:** None. **T. Nakadai:** None. **Y. Loh:** None. **Y. Lu:** None. **R.M. Bastle:** None. **O. Berton:** None. **H. Zebroski III:** None. **N. Alenina:** None. **M. Bader:** None. **N. Bhanu:** None. **H. Molina:** None. **B.A. Garcia:** None. **R.G. Roeder:** None. **L. Shen:** None. **H. Li:** None. **T.W. Muir:** None. **I. Maze:** None.

**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.17/I1

**Topic:** G.07. Other Psychiatric Disorders

**Support:** MQ15FIP100011, MQ: Transforming Mental Health Research Fellowship (PI - Maze)

**Title:** The role of histone serotonylation in neuronal plasticity and behavior

**Authors: *A. AL-KACHAK**[1], L. A. FARRELLY[1], C. MENARD[1], A. E. LEPACK[1], R. BASTLE[1], A. S. AGUSTINUS[2], Y. LU[1], A. TAN[1], S. J. RUSSO[1], Y. DAVID[2], I. MAZE[1]
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**Abstract:** The field of neuroepigenetics has grown rapidly over the past few decades, recently implicating chromatin phenomena in the etiology of several psychiatric disorders including

major depressive disorder (MDD). While it has been demonstrated that dysregulation of histone posttranslational modifications (PTMs) may be involved in the deleterious transcriptional processes that promote physiological maladaptations in MDD, underlying mechanisms contributing to this disorder are not fully understood. While it is clear that aberrant serotonergic signaling in brain plays a critical role in the pathophysiology and treatment of MDD, data from our laboratory suggest potential alternative mechanisms of action for monoamines-so-called histone monoaminylations-whereby, for example, the presence of serotonin in the nucleus of dorsal raphe (DR) neurons may directly mediate transcriptional responses related to serotonergic plasticity and MDD. Our preliminary data indicate that histone serotonylation is significantly altered in chronically stressed rodents and postmortem DR tissues from MDD subjects, phenomena that appear to be reversed by antidepressant treatments. Furthermore, potentiation of such alterations in a rodent model of MDD (e.g. chronic social defeat stress) enhances susceptibility to stress, indicating a functional role for histone serotonylation in depressive-like behaviors.
It has also been shown that there is a unique critical window of plasticity related to serotonergic neuronal development and circuit formation in rodents occurring during postnatal periods. Pharmacological manipulation of serotonin via fluoxetine precipitates depressive phenotypes in adulthood. Such findings support the notion that susceptibility to depression in adults may result from early life alterations in serotonergic signaling, and possibly, histone serotonylation itself. We therefore are performing developmental profiles (both transcriptional and epigenomic, +/- early life fluoxetine exposures) of serotonergic neurons to assess if histone serotonylation may have a role in neuronal development/maturation in relation to later life stress susceptibility. Considering that antidepressant treatments are only effective for ~1/3 of individuals with MDD, it will be important to develop novel approaches that target histone PTMs in a cell-type specific manner in vivo to better understand their direct contributions to disease states for development of future pharmacological interventions. Thus, we are now developing novel intein-based chemical methodologies to synthesize specific histone PTMs in brain for functional behavioral assessments.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

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**Program#/Poster#:** 472.18/I2

**Topic:** G.07. Other Psychiatric Disorders

**Support:** 2017 Basil O'Connor Starter Scholar Research Award March of Dimes

**Title:** Aberrant chromatin regulatory mechanisms in Down syndrome

**Authors: *Y. LU**[1], A. E. LEPACK[1], A. EAGLE[2], R. M. BASTLE[1], W. WENDERSKI[3], L. A. FARRELLY[1], J. STAFFORD[4], A. AL-KACHAK[1], S. FULTON[1], M. HEYER[1], H. MOLINA[5], R. CAO[6], A. BHATTACHARYYA[7], W. MOBLEY[8], P. J. KENNY[1], K. BRENNAND[1], R. ROPER[9], H. LI[6], A. FRIEDMAN[10], A. ROBISON[2], I. MAZE[1]
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**Abstract:** Down syndrome (DS) is the most common genetic cause of intellectual disability worldwide resulting from triplication of chromosome 21 (HSA21) in humans. Despite much progress in understanding the genetics of DS, the genes encoded on HSA21 that directly contribute to intellectual disability, as well as their associated molecular mechanisms, remain incompletely understood. BRWD1 is an uncharacterized, brain enriched chromatin effector protein encoded within the DS critical region 2 on HSA21. BRWD1 is believed to act as a transcriptional activator via its chromatin interactions (i.e., 'reading' functions); however, its roles in the contexts of neurodevelopment and in DS have yet to be studied. We recently observed that Brwd1 expression is significantly elevated in brain of two rodent models of DS, as well as in neurons derived from human induced pluripotent stem cells from DS subjects. Numerous associated histone posttranslational modifications (PTMs), many of which we have demonstrated to directly interact with BRWD1, are also altered in their expression. We have further demonstrated that Brwd1 overexpression, similar to that observed in DS-like brain, via viral-mediated transduction of adult dorsal hippocampal neurons (CA1) in wildtype animals results in a) a blockade of immediate early gene responses during contextual conditioning, b) abnormalities in neural physiology and c) deficits in cognition (both contextual and spatial memory). It is therefore our working hypothesis that BRWD1 trisomy in DS brain results in aberrant interactions between BRWD1 and an altered epigenetic landscape, thereby contributing to deficits in transcriptional plasticity and cognition. Taken together, these studies will aid in our global understanding of essential neuroepigenetic processes associated with brain plasticity.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.19/I3

**Topic:** G.07. Other Psychiatric Disorders

**Title:** Histone turnover and chromatin accessibility in Major Depressive Disorder (MDD)

**Authors: *S. L. FULTON**[1], J. FULLARD[1], T. HALENE[1], K. GLEASON[2], B. BUCHHOLZ[3], M. BIRTWISTLE[1], J. COPLAN[4], C. TAMMINGA[2], S. AKBARIAN[1], Y. DAVID[5], P. ROUSSOS[1], I. MAZE[1]
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**Abstract:** Throughout neurodevelopment and into adulthood, precisely coordinated spatiotemporal regulation of chromatin conformations and accessibility dictates the complex transcriptional programs required for neuronal maturation and function. As highly specialized postmitotic cells, neurons exhibit remarkable plasticity in response to external signals-a characteristic largely mediated by activity-dependent gene expression. Currently the processes that dynamically modulate nucleosome structure at activity-dependent loci are not well understood. Recently however, our laboratory described a novel mechanistic role for histone turnover in this brain-specific form of transcriptional plasticity. We found that the H3.3 histone variant accumulates in neuronal chromatin with age, remaining highly dynamic over time. Critically, H3.3 deposition into nucleosomes is required for activity-dependent gene expression, synaptic connectivity and cognition, suggesting that H3.3 incorporation may be a key mechanism maintaining neuronal function at both the synaptic and circuit levels. We now extend these findings to investigate the role of chromatin accessibility and H3.3 dynamics in neuropsychiatric disease states such as MDD. We build on our recent finding that disrupting H3.3 incorporation into the nucleosome results in aberrant transcriptional plasticity and increased susceptibility to depressive-like behaviors in the Chronic Social Defeat Stress (CSDS) mouse model. Importantly, we expand on the translational implications of this work by integrating measures of nucleosome dynamics across human, non-human primate and rodent cohorts. This approach will allow us to examine both conserved and divergent chromatin regulation patterns across species, as well as to determine the contributions of histone dynamics to depression-like syndromes. To assess differential histone turnover in human postmortem tissues from depressed patients *vs.* normal controls, we employed 14C/12C bomb pulse dating of HPLC-purified H3.3 from brain tissues via accelerator mass spectrometry. To assess genome-wide nucleosomal deposition patterns and chromatin accessibility in human (MDD), monkey (Variable Foraging Demand) and rodent

(CSDS) models of depression, we use ATAC-seq (assay for transposase-accessible chromatin coupled to next generation sequencing) on FACS-isolated neurons and glia. The current study will greatly advance understanding of how chromatin structural regulation affects nucleosome dynamics and gene expression in the context of MDD, and may also identify novel mediators of depression for future therapeutics development.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** G.07. Other Psychiatric Disorders

**Support:** NIH Grant DP1DA042078

NIH Grant T32DA007135

**Title:** Novel chemical methodology for identification of endogenously dopaminylated substrates in brain

**Authors: *R. M. BASTLE**[1], R. THOMPSON[3], A. E. LEPACK[1], L. A. FARRELLY[1], Y. LU[1], H. MOLINA[4], T. W. MUIR[3], I. S. MAZE[1,2]
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**Abstract:** Monoamines are often regarded as chemical messengers that act on extracellular surface-bound receptors in brain. However, recent work has demonstrated that non-vesicular monoamines also reside within neuronal nuclei and have a neurotransmitter-independent, intracellular functions, where they are capable of being enzymatically (i.e., post-translationally) added to specific glutamine-containing proteins via transamidation by the tissue transglutaminase 2 (TGM2) enzyme. Indeed, we have established that histone H3 is a robust substrate for monoaminylation and that this process is directly involved in transcriptional regulation, cell type-specific differentiation programs, and psychiatric phenotypes. Therefore, we hypothesized that other, non-histone proteins may similarly be monoaminylated to regulate aspects of their function. In order to selectively isolate monoaminylated proteins from brain tissues, we developed a novel endogenous chemical tagging method to specifically immunoprecipitate (IP) dopaminylated/norepinephrinylated proteins. This approach relies on the unique catechol

chemistry of dopamine/norepinephrine (which contain two hydroxyl groups on their aromatic rings), whereby their oxidation to meta-quinones allows for the cycloaddition of a bicyclononyne (BCN) desthiobiotin-conjugated probe to endogenously catechol-modified substrates. To initially validate this approach, we demonstrated that histone H3 can readily be IP'd from tissue culture lysates after exogenous application of dopamine. In validating our probe for use in brain, we found that H3 can similarly be IP'd from mouse ventral tegmental area (VTA) nuclear extracts. Next, to identify alternative endogenously dopaminylated protein targets in brain, we probed mouse VTA nuclei using liquid chromatography mass spectrometry (LC-MS/MS). Of the several proteins identified, we have validated calcium-responsive transactivator (Crest/Ss18l1) as a target. Interestingly, Crest is a member of the neuronal-specific nBAF complex that is involved in nucleosome remodeling and contains a glutamine-rich region that has recently been implicated in amyotrophic lateral sclerosis (ALS). Future studies will assess functions for Crest monoaminylation. Furthermore, we are also examining dopaminylation of proteins in other neuronal fractions (e.g., synaptosomes) and cell types (e.g., glia), thus highlighting the overall utility of this novel method and the exciting prospects of exploring new roles for monoamines in cellular plasticity.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.21/I5

**Topic:** G.07. Other Psychiatric Disorders

**Support:** DP1DA042078

**Title:** Functions for histone dopaminylation in cocaine-induced transcriptional and behavioral plasticity

**Authors: *A. LEPACK**[1], L. A. FARRELLY[2], C. WERNER[3], A. C. W. SMITH[2], Y. LU[2], R. THOMPSON[4], R. O'CONNOR[2], R. M. BASTLE[2], S. ZHANG[5], H. LI[5], Z. WANG[3], T. MUIR[4], D. DIETZ[3], P. J. KENNY[2], I. MAZE[2]
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**Abstract:** Drug abuse is characterized by loss of control over drug intake, as well as persistent drug-seeking behaviors, despite negative consequences to both the drug abuser and those directly

affected by their behavior. Given that drug addicts continue to crave and pursue drugs of abuse following extended periods of abstinence and/or treatment indicates that there must be life-long changes that occur in brain to promote these behavioral phenotypes. Persistent changes in neuronal gene expression are known to promote physiological alterations implicated in drug addiction. More recently, cell-type and brain region specific epigenetic mechanisms have also been demonstrated to regulate transcriptional programs contributing to addiction-like behaviors; however, our understanding of how these mechanisms mediate life-long addiction remains limited. Dopaminergic neurotransmission in the central nervous system plays a critical role in psychostimulant-induced neural plasticity, with alterations in dopamine production/function being implicated in both the development and treatment of substance abuse disorders. Although packaging of dopamine by the vesicular monoamine transporter is essential for numerous aspects of reward, recent data have demonstrated the additional presence of 'reserve' pools of extravesicular monoamines in the nucleus of monoamine producing neurons. Dopamine, as well as other monoamines, has previously been shown to form covalent bonds with certain cytoplasmic proteins catalyzed by the tissue Transglutaminase 2 enzyme. Our laboratory has recently identified histone proteins as robust substrates for dopaminylation *in vivo*, specifically on histone 3 glutamine 5 (H3Q5dop). In addition, our data demonstrate that chronic withdrawal from volitional administration of extended access to cocaine in rodents results in high levels of dopamine accumulation in the nucleus of dopamine producing neurons in the ventral tegmental area (VTA), as well as altered expression of Tgm2, the H3 dopaminylase, and a robust increase in histone dopaminylation. Furthermore, we have demonstrated that inhibiting dopaminylation in VTA is sufficient to block cocaine-seeking behaviors following extended withdrawal. Taken together, these potentially paradigm-shifting studies will aid in our understanding as to how monoamines, specifically dopamine, function in brain to regulate neurotransmission independent neuronal plasticity and cocaine-mediated behaviors.

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**Poster**

**472. Transcription and Translation in Plasticity: Gene Expression**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 472.22/I6

**Topic:** G.07. Other Psychiatric Disorders

**Support:** Simons Foundation Junior Fellowship

**Title:** H3K27M expression in neurons induces reversion to a more primitive molecular and functional state

**Authors: *J. STAFFORD**[1], A. LEPACK[2], C.-H. LEE[1], D. KHODAGHOLY[4], B. UEBERHEIDE[1], J. CHAPMAN[1], G. LEROY[1], D. REINBERG[1], I. S. MAZE[3]
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**Abstract:** A burgeoning literature suggests that mature, post-mitotic neurons can "dedifferentiate" into a pluripotent, proliferative state that may give rise to cancer stem cells and ultimately brain tumors. Diffuse intrinsic pontine glioma (DIPG) represent one universally fatal class of brain tumors that may be particularly vulnerable to neuronal dedifferentiation, as they are characterized by a proneuronal phenotype and arise at critical developmental periods when neurons are still undergoing cell fate specification. Approximately 80% of DIPG are further characterized by a methionine substitution at lysine 27 of histone H3 (K27M) that leads to inhibition of polycomb repressive complex 2 (PRC2) and loss of the H3K27 di- and tri-methylation marks that it catalyzes. Because PRC2 function is essential for neuronal fate specification, we hypothesized that loss and redistribution of K27me2-3 in the K27M context may cause maturing neurons to dedifferentiate, precipitate a cancer stem cell-like state and set the stage for later oncogenic events. Here, we used *in vitro* and *in vivo* neuronal models to interrogate the impact of K27M on chromatin dynamics, transcriptional programs, morphology and neuronal network formation. At the molecular level, we see that while histone turnover appears largely intact, there are profound global alterations in histone modification profiles that lead to a transcriptional signature suggestive of a more primitive, pluripotent state. In fact, we found that maturing neurons and DIPG are both more vulnerable to the inhibitory action of K27M on PRC2 than other cell types. Furthermore, functional and morphological hallmarks of neural network formation were markedly impaired in K27M bearing neurons, as was their ability to respond to stimulation. Together, our results suggest that K27M may force neurons into a more primitive state that then combine with later oncogenic events to produce a cancer stem cell-like state, which bears the hallmarks of universally fatal, treatment resistant DIPG.

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**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.01/I7

**Topic:** B.08. Synaptic Plasticity

**Title:** Evidence for presynaptic protein synthesis and its requirement to maintain neurotransmitter release at the calyx of Held nerve terminal

**Authors: M. S. SCARNATI**, *K. G. PARADISO
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**Abstract:** Presynaptic activity requires the synthesis, localization, interaction and maintenance of thousands of proteins that are typically thought to be synthesized in the soma and transported to synapses. However, several groups have demonstrated that some postsynaptic proteins can be locally synthesized at dendritic locations far from the cell body. Local protein synthesis at presynaptic terminals has recently been shown to occur at inhibitory neurons in mammalian brains, but additional evidence has been difficult to obtain, largely due to the small size of most nerve terminals. To better address this question, we are using the calyx of Held nerve terminal, located in the medial nucleus of the trapezoid body (MNTB) in the auditory brainstem. This large, glutamatergic presynaptic terminal forms a monosynaptic, axosomatic connection to MNTB principal cells, and is involved in sound localization. The size of this nerve terminal, combined with an ability to transmit at high frequencies, and the long distance from the cell body make this nerve terminal a good choice to test for local presynaptic protein synthesis. Using fluorescent non-canonical amino acid tagging (FUNCAT) to measure newly synthesized proteins, we find that synaptic activity can produce newly synthesized presynaptic proteins in the calyx of Held nerve terminal. To determine if ribosomes are present in this presynaptic terminal, we did immunofluorescence experiments. We find evidence for 5.8s rRNA, a major component of ribosomes, in the calyx of Held nerve terminal. Next, we used a nucleic acid stain that fluoresces upon binding to RNA. These dye indicates the presence of RNA in the calyx of Held nerve terminal. This indicates that the message and machinery for local protein synthesis are present at this nerve terminal. Finally, electrical recordings of synaptic activity indicate that a reduction in firing frequency or a delay in neurotransmitter release can occur following prolonged synaptic activity in the presence of protein synthesis inhibitors. Our results indicate that local protein synthesis can occur at this nerve terminal, and it appears to be necessary to maintain high levels of presynaptic activity. These findings indicate that presynaptic protein synthesis occurs and that it can be required to maintain neurotransmitter release at high firing frequencies.

**Disclosures: M.S. Scarnati:** None. **K.G. Paradiso:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.02/I8

**Topic:** B.08. Synaptic Plasticity

**Support:** R01-DA017392

R01-AG039521

F31-NS073200/T32-GM007288

**Title:** Linking cannabinoid-1 receptor activation to presynaptically-synthesized target proteins in endocannabinoid-mediated long-term plasticity

**Authors: *H. R. MONDAY**, T. J. YOUNTS, M. E. KLEIN, B. A. JORDAN, P. E. CASTILLO
Neurosci., Albert Einstein Col. of Med., Bronx, NY

**Abstract:** The ability of synapses to undergo changes in strength underlies information storage in the brain. The necessity of local postsynaptic protein synthesis in synaptic plasticity is well-established, but the role of presynaptic protein synthesis in the adult mammalian brain remains poorly understood. Using electrophysiology, fluorescent noncanonical amino acid tagging (FUNCAT) to visualize newly synthesized proteins, and super-resolution microscopy, we recently reported that endocannabinoid-mediated long-term depression of inhibitory transmission (eCB-iLTD) in the hippocampus requires presynaptic protein synthesis. We found that eCB-iLTD is blocked by inhibiting protein synthesis in the presynaptic neuron but not by inhibiting somatic translation or trafficking along microtubules, suggesting that translation in the presynaptic neuron occurs locally. In addition, using FUNCAT in hippocampal cultures, we discovered that activation of the cannabinoid-1 receptor ($CB_1R$) promotes protein synthesis. Here, we sought to determine the signaling pathways involved downstream of the $CB_1R$ that lead to and regulate protein translation. To this end we used a combination of approaches, including pharmacology and electrophysiology in rat hippocampal slices. We found that eCB-iLTD involves signaling via the Akt-GSK3-mTOR pathway, but unexpectedly, PI3K and $G_{\beta\gamma}$ are not required. We also used FUNCAT to test whether these pathways regulate $CB_1R$-dependent enhancement of new protein synthesis. In order to assess how protein synthesis regulates neurotransmitter release, we used stable isotope labeling of amino acids in cell culture (SILAC) and mass spectrometry as a first attempt to uncover target proteins whose expression is regulated by $CB_1R$ activation. Thus, we provide direct evidence that local presynaptic translation is a highly regulated process requiring a complex network of signaling molecules. The identification of key players in this signaling pathway linking sustained activation of the $CB_1R$ to the translation machinery may be important for developing therapies for diseases characterized by disrupted eCB-mediated plasticity, including schizophrenia, autism, and addiction.

**Disclosures: H.R. Monday:** None. **T.J. Younts:** None. **M.E. Klein:** None. **B.A. Jordan:** None. **P.E. Castillo:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.03/I9

**Topic:** B.08. Synaptic Plasticity

**Support:** NIH NRSA F31MH113310 (to WAH)

NIH R01MH077022 (to KCM)

**Title:** Systematic identification of activity-dependent synaptonuclear signaling proteins in the hippocampus

**Authors: *W. A. HERBST**, A. A. VASHISHT, A. K. RAJBHANDARI, M. S. FANSELOW, C. R. HOUSER, J. A. WOHLSCHLEGEL, K. C. MARTIN
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**Abstract:** New gene transcription is required to maintain long-lasting synaptic plasticity. This requirement for transcription indicates that signals from stimulated synapses must reach the nucleus, a target that is often hundreds of microns away. One such mechanism of synaptonuclear communication that is essential for long-term plasticity is the physical translocation of signaling proteins from the synapse to the nucleus. While a few dozen proteins are known to undergo activity-dependent synapse-to-nucleus translocation, little work has been done to systematically characterize the population of proteins that undergo this translocation. Here, we use several mass spectrometry-based approaches to identify proteins that undergo activity-dependent nuclear import. First, we identified cargoes of the importin β1 transport complex at the synapse. Importin β1 is a nuclear import protein that undergoes activity-dependent translocation from synapses to the nucleus in hippocampal neurons and its cargoes are likely to mediate synaptonculear communication. Mass spectrometry identified known as well as novel cargoes of importin β1 at the synapse. Next, we extracted nuclei from stimulated and unstimulated hippocampal neurons to identify proteins that exhibit activity-dependent nuclear localization. We used a strong stimulus (pilocarpine-induced seizures) and a weaker but more physiologically relevant stimulus (contextual fear conditioning). We first characterized the nuclear localization of a known synaptonuclear signaling protein, CRTC1, and are characterizing the population of syanptonuclear signaling proteins using mass spectrometry.

**Disclosures: W.A. Herbst:** None. **A.A. Vashisht:** None. **A.K. Rajbhandari:** None. **M.S. Fanselow:** None. **C.R. Houser:** None. **J.A. Wohlschlegel:** None. **K.C. Martin:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.04/I10

**Topic:** B.08. Synaptic Plasticity

**Support:** CIHR grant 258333

**Title:** Examination of stalled polysomes *In vivo* in hippocampal cultures

**Authors: *K. GINZBERG**, T. GRABER, W. SOSSIN
McGill Univ., Montreal, QC, Canada

**Abstract:** The stalled polysome model of mRNA transport in neurons describes the arrangement of mRNA cargo where the rate-limiting step of translation, initiation, occurs before transport (Graber et al, PNAS. 2013 Oct 1; 110(40): 6205-16210). The incomplete peptide is then transported to the dendrite, where, upon activation, translation recommences and protein synthesis is completed (Graber et al, 2013). Protein synthesis from stalled polysomes is necessary for metabotropic glutamate receptor mediated long term depression (mGluR-LTD) (Graber et al, 2013). In order to examine stalled polysomes in vivo in primary hippocampal cultures we have adapted Wang et al.'s (Cell. 2016 May 5;165(4):990-1001) suntagging technique (Tanenbaum et al, Cell. 2014 Oct 23; 159(3): 635-646.), which allows for real-time translation visualization using multivalent fluorescence amplification of a nascent polypeptide signal. A pre-formed GFP-ScFv molecule is expressed which binds to a simultaneously expressed nascent V4 peptide array during translation (Wang et al, 2016); the aggregation of GFP on the V4 array brings the signal above background. An ornithine decarboxylase at the C-terminus ensures the quick degradation of the construct upon translation completion; all signal is therefore derived from active sites of translation (Wang et al, 2016). We are comparing the translation dynamics of the V4 peptide to two modified V4 transcripts: one including the Arc 3'UTR and one including the Map1b 3'UTR: the 3'UTRS of Arc and Map1b mRNA transcripts have been implicated in the regulation of their localization and translation (Graber et al, 2013; Wang et al, 2016). The translation of Map1b following mGluR-LTD induction is initiation independent (Graber et al., 2013). Arc translation also increases following mGluR-LTD (Tatavarty et al, Mol Biol Cell. 2012 Mar 1; 23(5): 918-929); this translation appears to also be initiation independent, but in a manner dependent on its open reading frame and we thus do not expect to observe this effect in our reporter (Na et al, Neuron. 2016 Aug 3;91(3):561-73). We are examining the effects of the initiation inhibitor homoharingtonine (HHT) and DHPG-induced mGluR-LTD on the Map1b and Arc reporters described above. We expect increased dendritic localization of both reporters relative to the unmodified V4 transcript, and we expect signal from our Map1b reporter but not from our Arc reporter to persist in the presence of HHT. We also

expect that signal from our Map1b reporters will decrease with DHPG application regardless of HHT presence. Using these tools, we are able to further elucidate the mechanisms of stalled polysome-regulated mRNA transport.

**Disclosures: K. Ginzberg:** None. **T. Graber:** None. **W. Sossin:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.05/J1

**Topic:** B.08. Synaptic Plasticity

**Title:** The role of mTORC1 effectors eIF4A1 and PDCD4 in activity dependent translation

**Authors: *I. KATS**[1], E. KLANN[2]
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**Abstract:** *De novo* protein synthesis has been shown to be critical for long-lasting synaptic plastisticity as well as the formation of long-term memories. In contrast, dysregulated protein synthesis plays a role sbbrant behaviors associated with autism spectrum disorder. Translation initiation, regulated by mammalian target of rapamycin 1 (mTORC1) and its effectors eIF4E and p70 S6 kinase 1 (S6K1), are relevant to both normal function and disease. Incresed expression of eukaryotic initiation factor 4E (eIF4E) or deletion of its inhibitor eukaryotic factor 4E binding protein 2 (4E-BP2) causes autistic endophenotypes in mice. Moreover deletion of while S6K1 can cause deficits in various types of memory. Inhibitors of either the interaction of eIF4E with eukaryotic initiation factor 4G (eIF4G) or the eukaryotic initiation factor 4A (eIF4A) have also been shown to affect translation in brain slices and to disrupt long-term potentiation. eIF4A1, the helicase in the cap-dependent translation initiation complex, has proven to be important for translation in cancer cells and its inhibitor PDCD4 is phosphorylated and broken down by the proteasome pathway to allow for translation and cell growth. We have begun studies to examine the role of eIF4A1 and PDCD4 in activity-dependent translation. Our preliminary data indicate that PDCD4 is regulated by neuronal activity. Moreover, PDCD4 and eIF4A1 appear to have opposing effects of dendrite complexity in neurons. These results implicate the importance of eIF4A1 and PDCD4 in activity-dependent translation and regulation of dendritic morphology suggesting that they may play a role in memory function.

**Disclosures: I. Kats:** None. **E. Klann:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.06/J2

**Topic:** B.08. Synaptic Plasticity

**Support:** NIH Grant R01 DA034970

**Title:** Synaptic specificity in late long-term potentiation (L-LTP) is influenced the location of polyribosomes and protein dynamics

**Authors: *H. Z. SHOUVAL**[1], M. A. HUERTAS[2], T. C. SACKTOR[3]
[1]Neurobiol & Anat, Univ. Tex Medl Schl Houston, Houston, TX; [2]Neurobio. and Anat., Univ. of Texas Med. Sch. at Houston, Houston, TX; [3]Dept Physiol. & Pharmacol., SUNY Downstate Med. Ctr., Brooklyn, NY

**Abstract:** Memories that may last a lifetime are stored as persistent enhancement of synaptic efficacies, and the ability to preserve these over long time scales constitutes the maintenance phase of synaptic plasticity. The synaptic mechanism underlying these persistent changes, late long-term potentiation (L-LTP), depends on the state and number of specific synaptic proteins. These proteins are synthesized by polyribosomes located in dendritic shafts or inside synaptic spine's. Due to the diffusive nature of proteins in solutions, a question arises as to the possibility that proteins synthesized in one, previously stimulated, site might diffuse into a different location compromising synaptic specificity. This this is a general problem for maintenance by a bi-stable switch and applies specifically to maintenance by *PKMζ,* where evidence indicates that ongoing protein synthesis and slow degradation are essential for memory maintenance.
Previously we have shown (Aslam et al., 2009; Jalil et al., 2015) that positive feedback at the level of the translation can insure the stability of protein number after the induction of plasticity, despite diffusion and protein turnover. This approach can also account for the observed effect of kinase, and protein synthesis inhibitors in the induction of L-LTP and long-term memory. On the basis of this concept we develop a reaction-diffusion implementation of this model and investigated the conditions and limits of synapse specificity in this framework. Our results include both theoretical analysis and simulations performed using NEURON's Reaction-Diffusion (rxd) module in Python.
By exploring steady-state spatial distributions of synthesized proteins we determined the critical distance between polyribosomes at which synapse specificity is preserved and characterize how various morphological (e.g. spine neck diameter) and dynamical (e.g. degradation rate) parameters, and the location of polyribosomes, i.e. in dendrites outside of spines or inside spine heads, influence this critical separation. We also explore how the existence of immobile (or slowly diffusing) proteins in dendritic spine heads can contribute to improve synaptic specificity.

We conclude that if the protein synthesis, that is responsible for maintenance, occurs in dendritic shafts, synapse specificity as observed experimentally could not be maintained. On the other hand if protein synthesis occurs within synaptic spines, synapse specificity could feasibly be maintained by this maintenance mechanism. Therefore our model generates a strong prediction that synapses in which L-LTP has been induced should be populated with active polyribosomes.

**Disclosures: H.Z. Shouval:** None. **M.A. Huertas:** None. **T.C. Sacktor:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.07/J3

**Topic:** B.08. Synaptic Plasticity

**Support:** NIH Grant R01NS083085

NIH Fellowship F30CA214009

**Title:** The RNA binding protein ZBP1 regulates neuronal migration through control of beta actin mRNA

**Authors: *J. BISWAS**[1], Z. B. KATZ[2], A. R. BUXBAUM[3], M. LOPEZ-JONES[1], R. H. SINGER[1]
[1]Anat. and Structural Biol., Albert Einstein Col. of Med., Bronx, NY; [2]Salk Inst. for Biol. Studies, La Jolla, CA; [3]Neurosciences, Univ. of California San Diego, San Diego, CA

**Abstract:** During the early stages of neural patterning RNA binding proteins tightly regulate gene expression to facilitate cell survival, differentiation, and migration of neurons. Previous reports have elucidated the importance of the RNA binding protein Zipcode Binding Protein 1 (ZBP1) in RNA localization, axon guidance and directionality of cultured fibroblasts. However little has been done to elucidate its role in vivo. Here we report that ZBP1 acts as an essential component for neuronal development and migration through its role in actin regulation. Using a gene trap model we show that the expression profile of ZBP1 during development spatially and temporally coincides with regions of the brain important for the migration of newly differentiated neurons. Histopathological analyses and BrdU staining show an early cell organization deficiency in the developing neocortex and a loss of cell density in the cortical plate as well as the marginal zone of the cortex. To investigate the molecular mechanisms underlying these migration defects we focused our attention on how loss of ZBP1 may affect its best characterized target, beta actin. Our findings show that ZBP1 KO and knockdown not only affects the actin cytoskeleton and disrupts pools of F and G actin but affects actin transcription.

Taken together, our findings show that ZBP1 acts to guide persistent directionality of cells and reveals the importance of ZBP1 mediated actin RNA regulation in neural migration and survival.

**Disclosures: J. Biswas:** None. **Z.B. Katz:** None. **A.R. Buxbaum:** None. **M. Lopez-Jones:** None. **R.H. Singer:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.08/J4

**Topic:** B.08. Synaptic Plasticity

**Support:** NIH R01 NS086933-01

NIH R21 DA036673-01

Alzheimer's Association MNIRGDP-12-258900

Linda Crnic Institute

NIH T32 MH016880

**Title:** Investigating non-canonical translation in neurons

**Authors: *H. WONG**, J. LEVENGA, C. A. HOEFFER
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**Abstract:** Protein synthesis is required for persistent forms of synaptic plasticity such as long-term potentiation and long-term depression, which are thought to be cellular substrates of memory. The primary pathway for protein synthesis is canonical translation, which initiates with binding of the small ribosomal subunit and associated translation initiation factors to the 5' cap of eukaryotic mRNAs. While this pathway is well-studied and known to support synaptic plasticity and memory, protein synthesis can also occur to a lesser extent through non-canonical pathways. In one mode of non-canonical translation, protein synthesis initiates from an internal ribosome entry site (IRES) in the mRNA transcript. An IRES is a complex secondary structure in the mRNA that recruits the ribosome with an alternative set of translation initiation factors. Very little is known about the contribution of this IRES-mediated mode of translation to neural function. However, a few proteins critically linked to synaptic plasticity have been reported to contain an IRES in their mRNA transcript. We hypothesized that IRES-mediated translation may play a role in the protein synthesis supporting persistent forms of synaptic plasticity. To explore this idea, we have developed bicistronic translation reporters to measure cap- and IRES-mediated protein synthesis in neurons. Using these reporters in addition to complementary approaches, we

are examining translational activity in hippocampal neurons following different stimulation and treatment conditions. These studies may provide new insight into the translation mechanisms underlying synaptic plasticity and how their dysfunction could be involved in memory disorders.

**Disclosures: H. Wong:** None. **J. Levenga:** None. **C.A. Hoeffer:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.09/DP03/J5 (Dynamic Poster)

**Topic:** B.08. Synaptic Plasticity

**Title:** Ribosome intersubunit FLIM-FRET to detect ribosome assembly in dendrites

**Authors: *Y. J. YOON**[1], H. CHOI[3], R. H. SINGER[2]
[1]Anat. and Structural Biol., [2]Anat. & Structural Biol., Albert Einstein Col. of Med., Bronx, NY; [3]HHMI/Janelia Res. Campus, Ashburn, VA

**Abstract:** We have developed a ribosome intersubunit FRET assay that assesses the association of the small and large subunits of the ribosome in live cells. A pair of ribosomal proteins from each subunit were tagged with self-labeling HaloTag. The tag can be readily labeled with cell-permeable ligands conjugated to bright fluorescent dyes which allow single molecule detection. FRET was assessed using FLIM measurements to observe changes in fluorescence decay from fluorophores undergoing energy transfer. The results demonstrate that our FRET assay was able to detect clusters of assembled ribosomes within dendrites and reveal the presence of translating ribosomes or granules. An advantage of the FLIM-FRET assay is the ability to detect over time, which can reveal kinetic information about how polysomes or granules change.

**Disclosures: Y.J. Yoon:** None. **H. Choi:** None. **R.H. Singer:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.10/J6

**Topic:** B.08. Synaptic Plasticity

**Support:** SSTF-BA1602-11

**Title:** Dynamics of transcription and transport of labeled-endogenous Arc mRNA in live neurons

**Authors: *H. MOON**[1], S. DAS[2], R. H. SINGER[2,3], H. PARK[1]
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Anat. & Structural Biol., Albert Einstein Col. of Med., Bronx, NY; [3]Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA

**Abstract:** Spatially and temporally controlled gene expression is crucial for the formation of memory. Especially, an immediate early gene Arc is known to be deeply involved in the modulation of synaptic plasticity. Upon stimulation, transcription of Arc mRNA occurs in a selected group of neurons. After transcription, Arc mRNA is transported to the desired destinations including distal parts of dendrites for local translation. These two biological phenomena, transcription and transport of Arc mRNA undoubtedly have significant roles in the memory formation. We developed Arc-PBS KI mouse for single mRNA imaging in live cells by knocking in 24 tandem arrays of PP7 binding site (PBS) in the 3′ untranslated region (3′ UTR) of the Arc gene. Using the Arc-PBS KI mouse, we investigated the dynamics of transcription and the transport of Arc mRNAs in live primary neuron cultures. First, we simultaneously imaged somatic $Ca^{2+}$ activity and Arc mRNA transcription after stimulation by bicuculline. Whereas synchronized bursts of $Ca^{2+}$ activity was induced in 100% of neurons, Arc transcription was induced only in a subpopulation of neurons during 30 min of observation after stimulation. To determine the factor governing this selection of Arc transcribing neurons, we performed immunostaining of Ser-133 residue phosphorylated CREB and single molecule FISH of Arc mRNA together. We found that neurons with higher level of CREB phosphorylation (Ser-133) has indeed higher probability of Arc transcription. We also investigated transport of Arc mRNAs along the dendrites after stimulation. Most of the Arc mRNAs were in rest phase (~88%) during one-minute observation time, and even the directed motions of Arc mRNAs were frequently interrupted by rests, similar to the previously reported behavior of β-actin mRNAs. The active movements of Arc mRNAs were bidirectional with almost equivalent occurrence of anterograde and retrograde steps and with a speed of ~1.5 μm/s in both directions. In summary, this study presents new perspectives about the dynamics of transcription and transport of endogenous Arc mRNA, which plays important roles in synaptic plasticity at the molecular level.

**Disclosures: H. Moon:** None. **S. Das:** None. **R.H. Singer:** None. **H. Park:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.11/DP04/J7 (Dynamic Poster)

**Topic:** B.08. Synaptic Plasticity

**Support:** NIH Grant NS083085

**Title:** A transgenic mouse for visualizing dynamics of endogenous Arc (Arg3.1) mRNA in hippocampal neurons

**Authors: *S. DAS**[1], H. MOON[2], H. PARK[2], R. H. SINGER[1,3]
[1]Albert Einstein Col. of Med., Bronx, NY; [2]Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Janelia Res. Campus, Ashburn, VA

**Abstract:** Spatio-temporal control of gene expression in a neuronal network is an essential element of memory formation. The immediate early gene Arc (activity-regulated cytoskeletal associated), or Arg3.1, plays a crucial role in synaptic plasticity and memory consolidation. Arc expression is neuronal activity dependent and primarily regulated by transcription and targeting to active synapses. While most *in vivo* studies describe the spatial regulation of Arc, however, the temporal dynamics of single endogenous Arc mRNA in response to neuronal activity or LTP is not well defined. To address that, we have generated a transgenic mouse for tagging endogenous Arc gene by knocking in 24 repeats of bacteriophage-derived PP7 binding sites (PBS) into 3'UTR of Arc gene. These PBS stem-loops are bound by their cognate partner-PP7 coat protein (PCP), which are fluorescently labeled, thereby allowing visualization of active Arc loci and individual mRNAs in real-time. In hippocampal neurons from this mouse, by real-time imaging, we detect transcription from both endogenous Arc alleles, and observe transcriptional bursting in response to synchronous neuronal activity. Also, using single molecule fluorescence *in-situ*hybridization (smFISH), we can quantify the transcriptional burst from each allele, and mature Arc mRNA production with high spatial resolution. The tagging of endogenous Arc gene provides an important tool which will allow us to investigate the correlation between neuronal activity and endogenous gene transcription at single cell level with unprecedented spatio-temporal resolution.

**Disclosures: S. Das:** None. **H. Moon:** None. **H. Park:** None. **R.H. Singer:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.12/J8

**Topic:** B.08. Synaptic Plasticity

**Support:** US Department of Defense W81XWH011-1-038908-1-0508

**Title:** Altered protein synthesis and cortico-striatal synaptic function in Fragile X Syndrome (FXS) model mice

**Authors: *F. LONGO**[1], S. ARYAL[1,2], J. TABOR[2], E. SANTINI[3], E. KLANN[1]
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**Abstract:** Fragile X Syndrome (FXS) model mice display distinct repetitive/perseverative behaviors that are likely striatal-based (Welch et al., 2007), but the majority of studies on synaptic dysfunction in FXS model mice have been focused on hippocampal and cortical circuits. Altered protein synthesis appears to be a common molecular anomaly that contributes to synaptic and behavioral impairments associated with autism spectrum disorder (ASD). Consistent with this idea, patients with FXS, which is caused by the lack of the RNA binding protein fragile X mental retardation protein (FMRP), have a high incidence of ASD. Increased eIF4F complex formation measured as an increase in eIF4E-eIF4G interactions has been reported in FXS model mice, which may results in altered protein synthesis that could lead to abnormal cortico-striatal synaptic function and plasticity, and aberrant behavior in FXS model mice. The mechanism for the increased eIF4E-eIF4G interactions in FXS could be due to upregulated mTORC1 signaling (Sharma et al., 2010), disruption of FMRP/CYFIP1/eIF4E complexes (Napoli et al., 2008), or a contribution of both pathways, which would result in exaggerated cap-dependent protein synthesis (Hoeffer and Klann, 2010). Our central hypothesis is that the aberrant repetitive and perseverative behaviors exhibited by FXS individuals is due to exaggerated eIF4E-mediated translation at cortico-striatal synapses. Using FUNCAT to examine de novo protein synthesis, we found that FXS mice exhibited altered protein synthesis in the striatum. We proceeded to determine whether cortico-striatal synaptic composition, function, and plasticity were altered in FXS model mice, and found that high-frequency stimulation-induced metabotropic glutamate receptor (mGluR)-dependent long-term depression (LTD) in cortical-striatal slices from FXS model mice was enhanced. These findings are consistent with previous findings in hippocampal and cortico-striatal slices from eIF4E transgenic (Santini et al., 2013) and FXS model mice (Huber et al., 2002; Hou et al., 2006). Finally, repetitive behaviors in FXS model mice were reversed by the cap-dependent translation inhibitor 4EGI-1 (Moerke et al., 2007) that selectively disrupts the interaction between translation factors eIF4E and eIF4G. Our findings are consistent with the hypothesis that enhanced cap-dependent translation via increased eIF4E-eIF4G interactions contributes to repetitive behaviors displayed by FXS model mice that are likely cortico-striatal in nature and provide critical information concerning potential therapeutic treatments for synaptic and behavioral dysfunction not only FXS, but also in ASD.

**Disclosures: F. Longo:** None. **S. Aryal:** None. **J. Tabor:** None. **E. Santini:** None. **E. Klann:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.13/J9

**Topic:** B.07. Synaptic Transmission

**Support:** NIH Grant DA039533

**Title:** Epigenetic and synaptic modifications associated with severe early life stress in the ventral tegmental area

**Authors: *R. D. SHEPARD**[1,1], H. KASSIS[1], S. GOUTY[1], M. E. AUTHEMENT[1], L. D. LANGLOIS[2], C. A. BROWNE[4], I. LUCKI[3], B. M. COX[5], F. S. NUGENT[1]
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**Abstract:** Severe early life stressors increase the probability of developing psychiatric disorders later in life through modifications in neuronal circuits controlling brain monoaminergic signaling. Our previous work demonstrated that a single episode of maternal deprivation (MD, a 24hr deprivation on postnatal day 9) in rats modifies dopamine signaling from the ventral tegmental area (VTA) through changes at GABAergic synapses onto VTA dopamine neurons. These synaptic changes were reversible via in vitro histone deacetylase (HDAC) inhibition through restoration of the scaffold A-kinase anchoring protein (AKAP150) signaling that is important for $GABA_A$ receptor trafficking in VTA dopamine neurons. Our work here confirms that that MD induces epigenetic modifications at the level of histone acetylation (histone H3 hypoacetylation at lysine 9, Ac-H3K9) associated with an upregulation of HDAC2 (a class I HDAC). In vivo injection with a selective class 1 HDAC inhibitor, CI-994, was sufficient to reverse MD-induced hypoacetylation at 3hr and 24hr after the injection. Western blot analysis of AKAP150 expression through sub-cellular fractionation technique showed an increase in synaptic levels of AKAP protein in VTA tissues. Consistent with these results, we found that MD increased AKAP150 mRNA levels using in situ hybridization technique. Western blot analysis also confirmed that the protein levels of gephyrin and mature brain-derived neurotrophic factor (mBDNF) were lower after MD. On the other hand, NMDA receptor NR2B subunit expression was upregulated while NR2A protein levels were unchanged in the VTA after MD suggesting that the developmental switch of NMDA receptor composition in these young rats may be delayed. Our electrophysiological recordings of dopamine cell excitability in response to depolarizing currents showed that dopamine neurons were hyperexcitable after MD and this hyperactivity was normalized at 24hr after in vivo injection of the the HDAC inhibitor, CI-994. Behavioral analyses in the forced swim test in MD animals suggest that active coping climbing behavior was increased after MD. Future research will determine whether histone hypoacetylation occurs at gephrin and mBDNF promoters and whether a single in vivo injection of CI-994 is sufficient to reverse MD-induced epigenetic and synaptic modifications including the expression of AKAP150, gephrin, mBDNF, and NMDA receptor subunits in the VTA. Furthermore, we will investigate whether in vivo HDAC inhibition normalizes behavioral changes associated with MD.

**Disclosures:** **R.D. Shepard:** None. **H. Kassis:** None. **S. Gouty:** None. **M.E. Authement:** None. **L.D. Langlois:** None. **C.A. Browne:** None. **I. Lucki:** None. **B.M. Cox:** None. **F.S. Nugent:** None.

**Poster**

**473. Transcription and Translation in Plasticity: mRNA and Protein Dynamics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 473.14/J10

**Topic:** B.08. Synaptic Plasticity

**Support:** ERC Advanced Investigator grant (322744; LO)

Swedish Research Council (K2012-62X-03185-42-4; LO)

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StratNeuro

Wings for Life

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Swedish Brain Foundation (AJ)

**Title:** Activity-driven regulation of Nogo receptor 1 expression and localisation

**Authors: *A. T. BRODIN**, D. T. DOMINGUES, K. WELLFELT, L. OLSON, T. E. KARLSSON
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**Abstract:** Nogo receptor 1 (NgR1) together with multiple partners restrict plasticity during development and learning. Overexpression of NgR1 results in impaired long term memory and less elaborate dendritic trees. We and others have shown that NgR1 mRNA is downregulated by increased neural activity, and have hypothesized that this downregulation is a prerequisite for the formation of lasting memories. However, it is still unclear whether NgR1 acts presynaptically, postsynaptically, or at both locations. Further, while NgR1 mRNA is robustly downregulated by activity, it remains to be determined how this correlates to levels and locations of functional NgR1 protein. Finally, little is known about the signalling pathways from increased neuronal activity to alterations of NgR1 mRNA levels. Using primary hippocampal cell cultures, we are analysing the transcriptional and translational regulation of genes involved in Nogo-type signaling. Using several complementary techniques, we investigate how the different proteins are distributed with regard to pre- or postsynaptic localisation. We also show that altered neuronal activity significantly alters transcriptional activity of most of the investigated genes. The results

contribute to positioning the Nogo-system as a master regulatory system of activity induced structural plasticity and hence how memories are formed and maintained.

**Disclosures: A.T. Brodin:** None. **D.T. Domingues:** None. **K. Wellfelt:** None. **L. Olson:** None. **T.E. Karlsson:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.01/J11

**Topic:** B.09. Physiological Properties of Neurons

**Support:** CIHR Grant MOP-137072

CIHR Grant MOP-142447

**Title:** Network state-dependent recruitment of hippocampal CA1 interneuron-selective cells in awake mice

**Authors: *L. TOPOLNIK**, V. VILLETTE, R. FRANCAVILLA
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**Abstract:** In the CA1 hippocampus, type 3 interneuron-selective cells co-express vasoactive intestinal peptide (VIP) and calretinin and innervate selectively several different types of CA1 orien/alveus interneurons. Despite their potentially important role in coordination of network activity and hippocampus-dependent mnemonic processes through local circuit disinhibition, very little remains to be known about the functional organization of this cell type and its recruitment in awake animals in relation to network oscillations. To understand the functional role of IS3 cells, we performed *in vivo* two-photon calcium imaging of VIP interneuron activity in the CA1 hippocampus in combination with contralateral local field potential (LFP) recordings in head-restrained awake VIP-Cre mice running on the treadmill. During the experiment, mice showed spontaneous alternations in their behavior between locomotion periods that were associated with prominent theta oscillations and stationary states with occasional high-frequency ripple episodes. Putative IS3 cells identified *post-hoc* based on the soma properties and the expression of calretinin showed a high level of variability in somatic activity, but overall were more active during locomotion than during quiet state. Moreover, during theta oscillations associated with locomotion periods, IS3 cells often exhibited a delayed recruitment. During quiet state, these cells showed no change in somatic activity in relation to contralateral ripple episodes. Collectively, these data indicate that IS3 cells are preferentially recruited during theta-run epochs and, through timely disinhibition at different spatial domains of pyramidal cells, may facilitate the input integration and plasticity induction during animal navigation.

**Disclosures:** **L. Topolnik:** None. **V. Villette:** None. **R. Francavilla:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.02/J12

**Topic:** B.09. Physiological Properties of Neurons

**Support:** NIH

NSERC

Ontario Graduate Scholarship

**Title:** Constraining dendritic $I_h$ distributions in somatostatin-positive oriens-lacunosum/moleculare hippocampal interneurons using matched recordings and morphology

**Authors:** ***V. SEKULIC**[1,2], F. YI[4], T. GARRETT[5], F. K. SKINNER[1,3,2], J. J. LAWRENCE[6,7]
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**Abstract:** Inhibitory interneurons of the hippocampus are critical controllers of network rhythms that are linked to learning and memory. In particular, the oriens-lacunosum/moleculare (O-LM) cell directly regulates pyramidal cell activity in the hippocampal CA1 region. Thus, it is essential to understand how the biophysical properties of O-LM cells allow them to contribute to hippocampal function. Computational modelling is needed to synthesize experimental data and generate testable hypotheses. We previously developed O-LM models to study how biophysical properties of O-LM cells affect output. However, the models were developed using morphological and electrophysiological data obtained from different O-LM cells, resulting in non-uniqueness of the fitted model parameters. We hypothesized that experimental data of O-LM cells, with matched electrophysiological and morphological data, would result in constraints in dendritic distributions of hyperpolarization-activated, mixed cation channels ($I_h$). We performed a set of whole-cell recordings from dorsal hippocampal somatostatin-positive ($SOM^+$) O-LM cells in SOM-CRE/Rosa26YFP mice, followed by biocytin fills to match their electrotonic and morphological properties. We used Neuromantic to obtain 3D morphologies of the cells that served as the foundation for new multi-compartment O-LM cell models implemented in the NEURON simulation environment. The passive properties of the resulting models were fitted using current clamp data from the same cells. Surprisingly, we found that the

specific membrane capacitance across several O-LM cells was substantially lower than the values typically reported in mammalian neurons. Finally, we fitted the distribution of $I_h$ in the models as a function of distance from the soma using the PRAXIS optimization method in NEURON, while injecting the current clamp command data obtained from the experiments directly into the soma of the models. Interestingly, we found that the models were only able to fit the recorded membrane potential of O-LM cells in response to hyperpolarizing current steps when $I_h$ was distributed onto the majority of the dendrites. The fitted passive parameters, in conjunction with the recorded total membrane conductance due to $I_h$, thus provided robust constraints on the dendritic distributions of $I_h$ in $SOM^+$ O-LM cells. These results offer insights into the electrotonic structure of O-LM cells and dendritic distribution of HCN channels that impact on synaptic integration and spiking output. These models will serve as a next generation of tightly constrained O-LM cell models that can help obtain insight into hippocampal function.

**Disclosures: V. Sekulic:** None. **F. Yi:** None. **T. Garrett:** None. **F.K. Skinner:** None. **J.J. Lawrence:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.03/K1

**Topic:** B.09. Physiological Properties of Neurons

**Support:** NSERC Discovery Grant

CIHR

QEII-GSST

**Title:** Simulating *In vivo*-like states for hippocampal CA1 interneuron specific 3 cells

**Authors: *A. T. GUET-MCCREIGHT**[1,2], L. TOPOLNIK[4,5], F. K. SKINNER[1,2,3]
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**Abstract:** Obtaining recordings from individual cells during behaviour is technically challenging. This is more so for hippocampal interneuron subtypes which represent a neuronal minority and are difficult to unambiguously identify given interneuron diversities. Interneuron specific 3 (IS3) cells, a cell type known to exclusively inhibit other inhibitory interneurons, has yet to be characterized in terms of its function *in vivo*. Our goal here is to generate *in vivo*-like states for IS3 cells using our previously developed IS3 cell models to predict inputs that they

receive *in vivo* and, in concert with experiment, to understand their functional contributions to hippocampal activity.
We know that neurons *in vivo* show more depolarized membrane potentials ($V_m$), increased $V_m$ standard deviations ($\sigma_{Vm}$), and increased irregular spiking as measured by the coefficient of variation of interspike intervals (*ISICV*) relative to those *in vitro*. We use these criteria to determine conditions under which our models can exhibit high-conductance (HC), or *in vivo*-like, states. We started with two previously developed multi-compartment models of IS3 cells, experimentally-constrained synaptic parameters, and realistic synaptic density values. The first model variant (SDprox1), possesses ion channels in the soma and proximal dendrites including A-type potassium channels ($I_A$), whereas in the second model variant (SDprox2), $I_A$ is restricted to the soma.
We perform a parameter search where we vary the full range of synapse numbers and a wide range of presynaptic spike rates (~4.4 million simulations). We find that synchronous inputs (mainly excitatory) amplify the size of the HC state parameter spaces through increased *ISICV* and $\sigma_{Vm}$ values. On dividing the parameter space into high/low pools, we find that having (i) high excitation (783-1530 synapses; 20-30 Hz) and low inhibition (4-172 synapses; 10-50 Hz), or (ii) high inhibition (176-344 synapses; 60-100 Hz) and low excitation (18-765 synapses; 5-15 Hz), shifts the parameter space away from HC regimes. Also, SDprox2 mostly generated larger numbers of HC scenarios, likely due to the SDprox1 model having dendritic $I_A$, which reduces excitability.
Thus, we have shown that common inputs, balanced excitation/inhibition, and lack of dendritic $I_A$, promote HC states in IS3 cell models. We can further reduce possible HC scenarios by excluding levels of synaptic input that would render distal dendrites unresponsive due to saturation, and examining responsiveness to rhythmic inputs. Moving forward, these models will be used in combination with experimental work to obtain an understanding of the functional roles of IS3 cells in the hippocampus.

**Disclosures:** **A.T. Guet-Mccreight:** None. **L. Topolnik:** None. **F.K. Skinner:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.04/K2

**Topic:** B.09. Physiological Properties of Neurons

**Support:** CIHR Grant MOP-137072

**Title:** Properties of connections established by local and extrinsic excitatory projections on the hippocampal CA1 interneuron-specific interneurons

**Authors: *X. LUO**, R. FRANCAVILLA, L. TOPOLNIK
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**Abstract:** The information processing in cortical circuits requires a delicate balance between excitation and inhibition. In addition to the inhibitory interneurons that control the activation of pyramidal cells, there are interneuron specific (IS) interneurons that coordinate the network level of inhibition. In this study, we focused on the hippocampal CA1 Type 3 IS cells (IS3) that co-express the vasoactive intestinal peptide (VIP) and calretinin. These cells make synapses on several types of oriens/alveus (O/A) interneurons and may control the information flow through hippocampal CA1 area. However, the synaptic properties of local and extrinsic excitatory projections converging onto IS3 cells and the mechanisms of their recruitment during network activity remain unknown. Using a combination of patch-clamp whole-cell recording and electrical and optogenetic stimulation in CA1 area of acute hippocampal slices of VIP-eGFP and VIP-tdTomato mice, we examined the properties of local excitatory synapses on IS3 cells and of distant projections arriving from the median raphe (MR) nucleus. Our data showed that the excitatory postsynaptic currents (EPSCs) evoked in IS3 by activation of the temporoammonic pathway (TA) and the Schaffer collaterals (SC) had different amplitude, kinetics and temporal summation properties. In addition, both TA- and SC-EPSCs showed two components, which were mediated by the activation of AMPA and NMDA receptors, respectively. Furthermore, optogenetic activation of MR projections generated small EPSCs in some IS3 cells, consistent with sparse MR contacts on IS3 interneurons. In contrast, large-amplitude MR responses were evoked in other VIP cells located within the O/A including VIP basket cells. The MR-EPSCs were sensitive to both 5-$HT_3$ and glutamate receptor antagonists, consistent with viral targeting of both MR glutamate and 5-HT projections that innervated densely the CA1 LM and O/A layers. These data indicate that hippocampal IS3 interneurons are mostly recruited through SC- and TA-projections with distinct properties, which may be well suited for the activity-dependent coordination of hippocampal CA1 inhibition, induction of synaptic plasticity and gating of cortico-hippocampal information.

**Disclosures: X. Luo:** None. **R. Francavilla:** None. **L. Topolnik:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.05/K3

**Topic:** B.09. Physiological Properties of Neurons

**Support:** KAKENHI 16K15177

**Title:** Prolonged hyperexcitability of hippocampal mossy fibers after repetitive high frequency stimulation

**Authors: *H. KAMIYA**
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**Abstract:** Axons are classically thought to generate action potentials at the initial segments and propagate reliably to the target cells. However, recent studies suggested that the excitability of the axons and the terminals is regulated by the preceding neuronal activity in an activity-dependent manner, due to either modulation of the intrinsic properties of ionic channels or activation of the autoreceptors on the axonal membrane. In this study, it was attempted to test whether plastic changes in the axon excitability might be induced by repetitive stimuli of the input fibers. For this purpose, large axon terminals of hippocampal mossy fibers were adopted for monitoring axon excitability. Using a loose-patch recordings, axonal spikes were monitored directly from the single mossy fiber terminals. In the resting condition without stimulation, a very few spike was detected from the single axon terminals. However, repetitive high frequency stimulation of the mossy fibers (e.g. 100 Hz for 1 s, repeated 5 times) reliably increased the frequency of axonal spikes for prolonged time. In some recordings, burst discharges followed after the spike trains during the high-frequency stimulation, suggesting that axonal excitation outlasts the stimulation period. To look for the mechanism, local perfusion of $Ca^{2+}$-free solution around the recording site was used to minimize the contribution of autoreceptor activation. Application of $Ca^{2+}$-free solution diminished these burst discharges following high-frequency stimulation. This result suggests that activation of autoreceptors on the mossy fibers and/or the terminals causes the prolonged excitation. This activity-dependent hyperexcitability of axon may serve as a candidate cellular mechanism of epileptogenesis in the hippocampus.

**Disclosures: H. Kamiya:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.06/K4

**Topic:** B.09. Physiological Properties of Neurons

**Support:** Erna D. and Henry J. Leir Foundation

**Title:** Dominant role of $\alpha_1$ $Na^+/K^+$ ATPase in generating the slow afterhyperpolarization in CA1 pyramidal cells

**Authors: *M. N. TIWARI**, S. MOHAN, Y. BIALA, Y. YAARI
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**Abstract:** The slow afterhyperpolarization (sAHP) is a key regulator of intrinsic neuronal excitability. Changes in the sAHP have been implicated in learning behaviors, in cognitive

decline in aging, and in epileptogenesis. Despite its importance, its underlying mechanisms, traditionally attributed to $Ca^{2+}$-gated $K^+$ currents (IKCa's), are still controversial. Here, we have addressed the role of $Na^+/K^+$-ATPases (NKAs) in sAHP generation in rat CA1 pyramidal cells, using sharp glass microelectrode recordings in acute hippocampal slices perfused with standard aCSF (35$^o$C) containing synaptic transmission blockers. The sAHPs size increased with the number of spikes (5-150 spikes at 50 Hz). Suppression of IKCa's with $Ni^{2+}$ and $Cd^{2+}$ (200 μM each) had no significant effect on sAHPs evoked by up to 40 spikes, and only partially reduced the sAHPs evoked by longer spike trains. The sAHPs in aCSF containing $Ni^{2+}$ and $Cd^{2+}$ were inhibited by ouabain (10 μM) and by $K^+$-free aCSF, indicating that they are generated by NKAs. The size of NKA-sAHPs was voltage-dependent, increasing with depolarization and decreasing with hyperpolarization without reversing even at -115 mV. Low ouabain concentration (1 μM), that selectively blocks $\alpha_3$-NKA isoenzymes, had only a small effect on NKA-sAHPs. We conclude that in rat CA1 pyramidal cells, NKAs are the predominant generator of the sAHP, even in the case of sAHPs evoked by short spike trains. Of the two NKA isoenzymes expressed by CA1 pyramidal cells, namely $\alpha_1$- and $\alpha_3$-NKA, the former isoenzyme plays the dominant role in sAHP generation, endowing it with a steep voltage-dependence. Thus normal and pathological changes in $\alpha_1$-NKA expression or function may affect cognitive processes by modulating the inhibitory efficacy of the sAHP.

**Disclosures: M.N. Tiwari:** None. **S. Mohan:** None. **Y. Biala:** None. **Y. Yaari:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.07/K5

**Topic:** B.09. Physiological Properties of Neurons

**Title:** Activity dependent scaling of H-current in mouse CA1 OLM-interneurons

**Authors: *D. YOUSEF YENGEJ**, W. J. WADMAN
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**Abstract:** Activity driven homeostatic scaling of excitability is a well-documented way of keeping neuronal firing within working range. CA1 pyramidal neurons in the rat hippocampus adjust their excitability by upscaling hyperpolarization activated cyclic nucleotide-gated (HCN) channels in the membrane (van Welie et al., 2004; Noam, et al., 2010). H-current ($I_h$) was also found in CA1 interneurons, and while scaling of their current could have similar effects at the cellular level, the outcome at circuit level will be more complex. In this study, we investigated $I_h$ scaling in stratum Oriens-Laconusum-Moleculare (OLM) interneurons as a result of enhanced synaptic drive.
Whole cell patch-clamp recordings were performed in sagittal brain slices of 4-6 weeks old male

mice. OLM neurons were recognized based on location, morphology and high firing rate (>150 Hz). $I_h$ was quantified in voltage clamp by stepwise hyperpolarization. The voltage-dependent activation obeyed a Boltzmann function.
Alpha-Latrotoxin (LTX, 0.15 nM) was used to upregulate spontaneous synaptic release, which was confirmed by an enhanced presence of miniature post synaptic currents. As a consequence of the enhanced activation of the glutamatergic input, $I_h$ was upregulated in about 15 min. by approximately 51% (±11% SEM, n=9) in CA1 OLM-interneurons, in a way comparable to what has been described for $I_h$ upregulation in CA1 pyramidal neurons. The change was best described by amplitude scaling and did not affect the voltage dependent properties of $I_h$.
Neuronal sub-threshold resonance was measured by injecting a chirp current (0.5 - 20Hz) and recording the resulting membrane voltage response. Resonance was voltage dependent and most prominent around a membrane potential of -80 mV; it was blocked by the HCN channel blocker ZD7288 (20 µM). Preliminary results indicate that $I_h$ scaling is associated with a change in resonance in OLM interneurons: The peak frequency of the resonance shifted with $I_h$ upregulation from ~2.0 Hz to ~2.9 Hz (n=3).
We conclude that OLM interneurons present activity induced scaling of $I_h$ which modulates intrinsic excitability, firing rate and subthreshold neuronal resonance. $I_h$ modulation in OLM interneurons will affect theta frequency and power (Neymotin, et al., 2013). Disruptions of this process could result in several disorders, including epilepsy.
Neymotin, S. A., *et al.* Y., PLoS ONE, 2013.
Noam, Y. *et al.* Journal of Biological Chemistry, 2010.
van Welie, I., *et al.* PNAS, 2004.

**Disclosures: D. Yousef Yengej:** None. **W.J. Wadman:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.08/K6

**Topic:** B.09. Physiological Properties of Neurons

**Support:** the College of Medicine, University of Arkansas for Medical Sciences (startup funding to S.-H.L.)

NIH Grant P30 GM110702

**Title:** Group I metabotropic glutamate receptors generate two types of intrinsic membrane oscillations in hippocampal O-LM interneurons

**Authors: G. GOVINDAIAH**[1], Y.-J. KANG[1], L. CHUNG[3], E. GARCIA-RILL[2], *S.-H. LEE[1]
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of Arkansas For Med. Sci., Little Rock, AR; [3]Dept. of Neurobio., Duke Univ. Sch. of Med., Durham, NC

**Abstract:** Metabotropic glutamate receptors (mGluRs) are a family of G protein-coupled receptors, and are highly expressed in the hippocampus. Activation of hippocampal group I mGluRs (i.e., $mGluR_1$ and $mGluR_5$) is known to regulate interneuron excitability and synaptic transmission, and generate network oscillations. In addition, previous studies have shown that activation of mGluRs produced slow supra-threshold membrane oscillations (< 0.1 Hz) in oriens-lacunosum moleculare (O-LM) interneurons. The underlying mechanisms at the single cell level of gamma and slow oscillations are not fully understood. We have examined key factors in regulation of intrinsic slow and gamma oscillations by using whole-cell patch-clamp recordings from identified CA1 O-LM interneurons. Our study revealed that the selective $mGluR_{1/5}$ agonist (S)-3,5-dihydroxyphenylglycine (DHPG) induced slow intrinsic membrane oscillations (< 0.1 Hz), which consisted of membrane depolarization and repolarization phases. DHPG produced supra-threshold membrane depolarization, which was associated with gamma frequency action potentials followed by action potential-free intrinsic gamma oscillations. The voltage-gated $Na^+$ channel blocker, TTX, blocked intrinsic gamma oscillations, while DHPG-induced slow oscillations were insensitive to TTX. The slow oscillations were reduced by the $mGluR_1$-selective antagonist LY341495, and were partially blocked by the $mGluR_5$-specific antagonist MPEP. Blockade of nonselective cation-conducting transient receptor potential channels or voltage-dependent L-type $Ca^{2+}$ channels blocked the slow oscillations. Depleting intracellular $Ca^{2+}$ with BAPTA or inhibiting ryanodine receptor-sensitive internal stores with ryanodine also abolished the slow oscillations. These findings suggest that DHPG induced two types of membrane oscillations in O-LM interneurons via multiple mechanisms. Our findings suggest that the activation of group 1 mGluRs in O-LM interneurons play an important role in regulation of hippocampal network oscillations, which support key functions of the hippocampus. This work was supported by the College of Medicine, University of Arkansas for Medical Sciences (startup funding to S.-H.L.), and a Center for Translational Neuroscience award from the IDeA program at NIGMS, P30 GM110702.

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**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.09/K7

**Topic:** B.09. Physiological Properties of Neurons

**Support:** DFG (SFB1134, Project A01)

**Title:** Local circuitry in the medial entorhinal cortex layer V

**Authors: *A. V. EGOROV**, F. S. LORENZ, A. ROZOV, A. DRAGUHN
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**Abstract:** The entorhinal cortex (EC) constitutes an important interface between the hippocampus and various regions of the neocortex. Sensory signals enter the hippocampal formation via neurons located in superficial layers of the EC. In turn, information from the hippocampus reaches the neocortex through deep layers of the EC (mainly layer V (LV)). Based on distinct molecular markers, LV of the medial entorhinal cortex (mEC) can be subdivided into layers Va and Vb. The main targets of projections from CA1 and the subiculum are Ctip2 positive pyramidal-like neurons in LVb. In contrast, Etv1 positive neurons with a characteristic horizontal basal dendritic tree located in LVa (i.e., a narrow zone adjacent to lamina dissecans) are the major source of intra-telencephalic projections. Here, we investigated the functional connectivity between CA1 and mEC LV neurons as well as the local connectivity within LV. We performed simultaneous paired patch-clamp recordings from LV neurons in acute horizontal mouse brain slices. Location and morphology of recorded neurons were confirmed by biocytin labeling and Ctip2 immunoreactivity. We found that electrical stimulation of the alveus in CA1 induced robust excitatory postsynaptic potentials (EPSPs) in identified layer Vb and Va principal neurons after a delay of ~ 4 ms, suggesting direct hippocampal input to both cell types. We found no evidence for direct synaptic connections from Vb to Va neurons (0/27 pairs). However, Va neurons were mutually interconnected with a probability of about 20% (5/26), while connectivity from Va to Vb cells was less than 5% (1/27). Additionally, we identified two types of local interneurons: fast-spiking (FS) and low-threshold spiking (LTS) interneuron. Remarkably, both types of interneurons also received monosynaptic hippocampal excitatory input as well as direct input from Va principal neurons. FS interneurons almost exclusively target Vb cells with high connectivity (4/6 pairs). Morphological analysis of principal neurons shows that all Vb cells are pyramidal shaped, while Va neurons revealed pyramidal as well as non-pyramidal forms (in 18%). The axon of both types of Va neurons exposed powerful arborizations within LV, as well as projections towards the angular bundle. Moreover, non-pyramidal Va neurons frequently send additional axonal branches towards superficial layers. We conclude that Va and Vb neurons as well as local interneurons receive direct input from CA1. Furthermore, our results indicate input-output integration by interconnected mEC LVa neurons and distinct signal processing within LV.

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**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.10/K8

**Topic:** B.09. Physiological Properties of Neurons

**Support:** SFB 1134: Functional Ensembles

**Title:** Privileged recruitment of axon-carrying dendrite pyramidal cells in hippocampal network oscillations

**Authors: M. E. KAISER**[1], T. SACKMANN[1], M. ENGELHARDT[2], L. LANDECK[1], P. GESCHWILL[1], A. DRAGUHN[1], C. SCHULTZ[2], *M. BOTH[1]
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**Abstract:** Exploratory behavior leads to the location-specific activation of hippocampal place cells. During memory consolidation at rest, these cells are then replayed in the same firing sequences but temporally compressed. In vitro this reactivation can be observed as hippocampal local field potential events of duration 30-60 ms called sharp-wave ripple complexes (SPWs). Recent studies postulate multiple mechanisms for forming such ensembles. For instance, recurrent excitatory feedback connections within the hippocampus enable reverberating activation without external inputs. Also, patterns of convergent and divergent synaptic connectivity, activity-dependent synaptic efficacy and non-linear dendritic integration support the formation of defined spatiotemporal activity of specific cells and while silencing neighboring neurons.
Recently, we showed that in about 50 % of CA1 hippocampal pyramidal cells the axon stems from a basal dendrite (axon-carrying dendrite cells, AcD cells) rather than from the soma (nonAcD cells). AcD cells are intrinsically more excitable and generate dendritic spikes with higher probability and greater strength. Axon-carrying dendrites for their part might constitute a privileged channel for excitatory synaptic input in this subset of cortical pyramidal cells. Consequently, this anatomical feature could represent a novel mechanism for neuronal networks to selectively recruit specific neurons into transiently stable ensembles and thereby promote specificity of neuronal representation.
However, the question whether AcD cells are preferentially recruited into multi-neuronal ensembles has yet to be addressed. We employed extra- and intracellular electrophysiological recordings as well as immunofluorescent stainings in acute hippocampal mouse brain slices. Our data suggests that network input to privileged dendrites potentially circumvents strong perisomatic inhibition that affects the cell during spontaneous SPWs. Indeed, our electrophysiological recordings indicate that only AcD cells were able to fire action potentials (APs) during spontaneous SPWs. These APs showed the peculiar waveform resembling ectopically generated spikes described previously. Both AcD cells and nonAcD cells received strong hyperpolarizing inputs, preventing classical APs from being generated. On the network level AcD cells appear to be recruited into neuronal ensemble activity preferentially.

**Disclosures:** **M.E. Kaiser:** None. **T. Sackmann:** None. **M. Engelhardt:** None. **L. Landeck:** None. **P. Geschwill:** None. **A. Draguhn:** None. **C. Schultz:** None. **M. Both:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.11/K9

**Topic:** B.09. Physiological Properties of Neurons

**Support:** the National Research Foundation of Korea (NRF) grant (2014051826)

**Title:** Kv4.1 is a key player for sparse firing of mature granule cells in hippocampal dentate gyrus

**Authors: *K.-R. KIM**[1], Y. SUH[2], S.-H. LEE[3], W.-K. HO[4]
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**Abstract:** The dentate gyrus (DG) hippocampal region is one of the most plastic regions where adult neurogenesis occurs. Another distinguishing characteristic of DG is sparse action potential firing. Firing of DG granule cells (DG-GCs) depends both on their synaptic connectivity and on low intrinsic excitability. However, the ion channel mechanism for low intrinsic excitability and its change during maturation are not well understood. Here, we show that Kv4.1 channels are preferentially expressed in DG-GCs among three major hippocampal regions, and its expression is increased with maturation. Functional analysis showed that blocking Kv4.1 channels with its specific antibody increased firing rates selectively in mature DG-GCs without affecting other parameters of intrinsic excitability, suggesting that Kv4.1 could in principle contribute to low intrinsic excitability in mature DG-GCs. Detailed analysis showed that Kv4.1-mediated currents in DG-GCs have distinct inactivation kinetics from A-type $K^+$ channels and a unique $Ca^{2+}$ sensitivity, in that its activity is inhibited by 10 mM BAPTA. Consistent with the specific localization of Kv4.1, its inhibition with antibody or 10 mM BAPTA have no effect in young DG-GCs or CA1 pyramidal neurons. Together, these data suggest that Kv4.1 channels act as a regulator to prevent hyperexcitability of mature granule cells. The action of Kv4.1 channels depends on the degree of intracellular $Ca^{2+}$ buffering, implicating a dynamic role of intracellular signaling in refining DG excitability.

**Disclosures:** **K. Kim:** A. Employment/Salary (full or part-time):; Postdoctoral researcher. **Y. Suh:** None. **S. Lee:** None. **W. Ho:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.12/K10

**Topic:** B.09. Physiological Properties of Neurons

**Title:** Retroaxonal barrage firing in neuropeptide Y interneurons in hippocampus and cerebral cortex

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**Abstract:** A novel form of persistent firing, originating from distal axons, has been reported previously in a subset of interneurons that contain neuropeptide Y (NPY cells) in the hippocampus CA1 area and piriform cortex (Sheffield et al. 2011, Krook-Magnuson et al. 2011 and Suzuki et al. 2014). We refer to this as retroaxonal barrage (RaB) firing, because it is generated in the distal axons of these cells (Sheffield et al. 2011). Although different subpopulations of interneurons in various brain areas express NPY, the ubiquity of such RaB firing has not been explored in them. To explore this possibility, patch clamp recordings were made from NPY interneurons in several areas of the hippocampus and neocortex. All recordings were made from parasagittal slices in mice expressing GFP under the NPY promoter and repetitive depolarization steps were used to induce RaB firing. RaB firing was observed in NPY cells in all layers of hippocampal areas CA1, CA2 and CA3. RaB firing was most frequently found in cells located near the border of SLM/SR of CA1. It was also observed in the subiculum, albeit in a lower fraction of cells (~33% of NPY cells) in this region compared to other hippocampal areas (~80%). We recorded from unlabeled interneurons in CA1, and could not induce RaB firing in any of them. In the cerebral cortex, all regions showed barrage firing (somatosensory, motor, orbitofrontal and visual cortices) with the highest percentages in the somatosensory cortex (~80%) and the lowest in the motor cortex (~67%). A large variability was observed between the duration of RaB firing in different regions, with a shorter median duration of RaB firing in the neocortex (median = 6.3 seconds) compared to the hippocampus (median = 18 seconds, Welch Two Sample t-test, $p = 0.029$). However, we could not find a significant difference between areas in the number of action potentials needed to induce RaB firing. Finally, in CA1, repeated induction of barrage firing in the same interneuron resulted in an increase in the duration of barrage firing from 5.5 s (first induction median duration) to 16.4 s on the fifth induction, but there was no change in the number of action potentials required to induce RaB firing. Together, these results suggest that barrage firing is a general phenomenon in the diverse group of NPY expressing interneurons in all hippocampal and many neocortical regions. This

finding has important implications regarding the potential functional consequences of RaB firing in cortical circuits.

**Disclosures:** **T. Deemyad:** None. **J. Lüthi:** None. **J. Winnubst:** None. **N. Spruston:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.13/K11

**Topic:** B.09. Physiological Properties of Neurons

**Support:** NSERC Grant 2014-05407

FRQ-S Groupe de Recherche

**Title:** Effects of dopamine on persistent firing in layer III entorhinal cortex neurons

**Authors: *A. A. BATALLAN BURROWES**, C. A. CHAPMAN
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**Abstract:** Persistent neuronal firing in entorhinal cortex neurons that occurs following depolarizing current injection is thought to provide a potential mechanism that could contribute to short-term working memory. Persistent firing is observed during muscarinic cholinergic receptor activation following periods of induced spiking, and is dependent on activation of the calcium-activated non-specific cationic current (CAN). Persistent firing is observed for varying durations in entorhinal layer cortex layer II, III, and V cells, and firing patterns reported previously in layer III cells are robust and long-lasting. Dopamine may contribute to mechanisms of working memory in the entorhinal cortex, and has been shown to modulate up and down states in layer III entorhinal neurons. Application of dopamine to entorhinal neurons can also result in increases in intracellular calcium that could modulate activation of the CAN current and the resulting persistent firing. We therefore used whole cell recordings to assess the effects of dopamine on persistent firing in layer III neurons initiated by strong depolarizing current steps. Slices from male Long-Evans rats (3 to 7 weeks-old) were maintained in ACSF (32 °C) containing kynurenic acid (2 mM) and picrotoxin (100 µM) to block excitatory and inhibitory synaptic transmission, and 4 sec, 50-300 pA current steps were used to induce persistent firing. Persistent firing was not observed in normal ACSF, but was observed in the presence of 10 µM carbachol in 16 of 37 layer III cells. Persistent firing occurred with a mean latency of ~4 sec following current injection, was associated with a mean plateau potential of ~4 mV, and lasted for 5 to >25 sec. Addition of 1 µM dopamine in 8 cells had variable effects on persistent firing. In 4 cells, persistent firing was no longer observed following addition of dopamine. In the remaining cells, there was a non-significant reduction in the amplitude of the plateau potential,

and no consistent changes in latency, duration, and frequency of persistent firing. These results indicate variability in the ability of layer III entorhinal neurons to display persistent firing, and also indicate that dopamine may suppress persistent firing in some entorhinal layer III neurons.

**Disclosures: A.A. Batallan Burrowes:** None. **C.A. Chapman:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.14/K12

**Topic:** B.09. Physiological Properties of Neurons

**Support:** Wellcome Trust, International Senior Research Fellowship #087497

Hungarian Academy of Sciences (Lendület Initiative #LP-2009–009)

Hungarian Brain Research Program (KTIA_13_NAP-A-I/5)

**Title:** Functionally distinct populations within anatomically similar CCK-expressing hippocampal interneurons

**Authors: V. OLAH**[1], D. LUKACSOVICH[2], J. WINTERER[2], C. FOLDY[2], Z. NUSSER[1], *J. SZABADICS[1]
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**Abstract:** Despite the substantial diversity in the firing properties of individual neurons, these activity patterns are homogeneous within a well-defined types of neurons. Here we provide evidences for an exception in this generally accepted view by demonstrating markedly different firing properties within an anatomically stereotyped group of hippocampal GABAergic cells. First, using *in vitro* patch-clamp recordings, we distinguished two subgroups of CCK-expressing interneurons (CCK-IN) based on their firing patterns in response to current injections. The first group of CCK-INs (TOR cells) showed rectifying activity with delayed onset firing during sustained current injections depending on the preceding membrane voltage. The second subset of morphologically indistinguishable CCK-INs did not show state-dependent spike inhibition (non-TOR cells), but they possessed regular firing, irrespective of the membrane potential preceding the activity. Voltage-clamp recordings revealed that the state-dependent rectifying firing is correlated with the presence of an A-type $K^+$ current that activates and inactivates at negatively shifted voltages. The pharmacological sensitivity and voltage-dependence of this $K^+$-current are consistent with the properties of Kv4.3 subunit-containing channels. However, immunolocalization experiments revealed the Kv4.3 subunit at a similar levels in TOR and nonTOR CCK+ cells. Therefore, we further explored the potential underlying differences

between the two subgroups by analyzing the total RNA content of individually recorded CCK+ cells using single cell RNAseq. This analysis suggested many differences in important neuronal genes including a distinguishing marker, SATB1, whose presence was verified in TOR, but not in non-TOR cells using immunolocalization. Furthermore, the results also showed that albeit the Kv4.3 RNA can be similarly detected in TOR and non-TOR CCK-INs, the auxiliary subunits of Kv4.3 channels, the KChIPs are remarkably different. Due to the known influence of KChIPs on currents conducted through the Kv4.3 channels, their differential availability in the two CCK-IN subgroups potentially explains the measured differences in the firing properties. Finally, we explored how these different A-current properties accommodate the excitability of otherwise similar neurons for various physiologically relevant activity regimes, such as theta-modulated inputs. Our results revealed that different availability of an A-type $K^+$ conductance could render different function among anatomically similar CCK-INs.

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**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.15/L1

**Topic:** B.09. Physiological Properties of Neurons

**Support:** UT Austin Institute for Neuroscience Training Grant

National Science Foundation CAREER Award #1453756

**Title:** Changes in firing rates of CA3 place cells across sleep following a novel experience

**Authors: *E. HWAUN**[1], L. L. COLGIN[2]
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**Abstract:** Encoding memories of new experiences presumably requires strengthening of synaptic connections between hippocampal neurons. However, without a regulatory mechanism, the overall excitability of the hippocampal network will continue to increase as more novel information is encoded. It has been hypothesized that neural activity levels are reset during sleep in order to preserve a relatively constant level of excitability over time. Accordingly, a previous study showed that neurons in hippocampal subregion CA1 decreased their firing rates during rapid eye movement (REM) sleep (Grosmark et al., 2012). However, it remains unclear whether firing rate reductions during REM are specific to cells encoding new experiences. Moreover, memories are thought to be stored in the recurrent collateral system of CA3, yet it is unclear whether similar firing rate changes occur in CA3. To address these questions, we recorded neural

activity in CA3 as rats were exposed to a novel environment and during the subsequent night's sleep. CA3 place cells that were active in the novel environment showed firing rate reductions during REM sleep, whereas firing rates of CA3 place cells that were not active in the novel environment did not change much during REM sleep. Moreover, firing rates during sharp wave-ripples in non-REM sleep were significantly higher for CA3 cells that were active in the novel environment compared to CA3 cells that were not active in the novel environment. Also, the magnitude of firing rate decreases during REM sleep was significantly correlated with the magnitude of firing rate increases during ripples. Together, these results suggest that homeostatic regulation of neural activity levels in CA3 cells during sleep is stronger for those cells that encode memories of new experiences that occurred earlier in the day.

**Disclosures: E. Hwaun:** None. **L.L. Colgin:** None.

**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.16/L2

**Topic:** B.09. Physiological Properties of Neurons

**Support:** Marquette University Committee on Research

Marquette University Dept. of Biological Sciences

**Title:** The role of calcium activated potassium channels in controlling excitability of neonatal hippocampal neurons in primary cultures

**Authors: M. S. HUNSBERGER**, A. J. MONICAL, *M. MYNLIEFF
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**Abstract:** Profound differences in excitability exist between the adult and neonatal hippocampus. These differences may be partly due to differences in the complement of potassium ($K^+$) channels expressed in adults and neonates. We examined the contributions of specific $K^+$ currents to the regulation of excitability in neonatal neurons. $K^+$ channels regulate excitability by determining speed of action potential (AP) repolarization as well as the magnitude and duration of the fast, medium, and slow afterhyperpolarizations (fAHP, mAHP, and sAHP). Whole-cell patch clamp recordings in current clamp and voltage clamp mode were performed on primary cultures of neonatal rat (P0-P10) hippocampal neurons. Cells were categorized into four general groups (basket, stellate, vertical, and pyramidal) according to the duration of their AP, the fAHP, and maximum firing rate in response to a 100 ms depolarizing pulse. Recordings were performed in the presence of nimodipine to determine the role of the L-type Calcium ($Ca^{2+}$) current in regulating excitability through activation of $Ca^{2+}$ activated $K^+$ channels and specific $K^+$

channel blockers to determine the roles of individual $K^+$ currents across cell types. Nimodipine (10 µM) blocked 66% of the sustained $K^+$ current ($I_K$; N=31), 25% of the transient $K^+$ current ($I_A$; N=25), and decreased the duration of the AP across all cell types (N=42; p=0.016). Nimodipine treatment decreased the magnitude of the fAHP in basket and stellate cells but not in the other cell types identified. This confirmed that $Ca^{2+}$ influx through L-type channels contributes to excitability in neonatal hippocampal neurons, likely due to activation of $K^+$ channels. Blockade of the large conductance BK channels with 100 nM verruculogen resulted in an attenuation of 15% of $I_K$ (N=30) and 23% of $I_A$ (n=25). Verruculogen decreased AP trains by 24% in response to a 1s pulse (N=21) and also decreased the magnitude of the mAHP after a 100 ms pulse by 14% in basket cells (N=5). Blockade of the small conductance SK channels with 1 µM apamin resulted in an attenuation of 21% of $I_K$ (N=30) and 24% of $I_A$ (N=27). These data suggest that the potassium current blocked by the L-type channel blocker, nimodipine, is likely comprised of multiple $Ca^{2+}$ activated $K^+$ currents. The effect of blockade of KCNQ channels was also tested as these channels are suggested to be both voltage gated and $Ca^{2+}$ sensitive. Blockade of KCNQ channels with 50 µM XE-991 resulted in an attenuation of 64% of $I_K$ (N=19) and 54% of $I_A$ (N=18). The larger blockade of $I_A$ by BK, SK, and KCNQ blockers when compared to blockade of L-type $Ca^{2+}$ channels suggests that other $Ca^{2+}$ channels contribute specifically to the transient portion of the $K^+$ current in these cells.

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**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.17/L3

**Topic:** B.09. Physiological Properties of Neurons

**Support:** NIMH grant R01_MH64711

NINDS grant R56_NS085330

NIH Grant 23945

**Title:** Ionic current correlations are ubiquitous and regulated - evidence from mammalian neurons

**Authors: *J. P. GOLOWASCH**[1], T. TRAN[3], C. T. UNAL[4], L. ZABORSZKY[4], H. G. ROTSTEIN[2], A. KIRKWOOD[3]
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**Abstract:** Ionic current levels in populations of identical neurons are extremely variable (Goldman et al. 2001; Leao et al. 2012; Liss et al. 2001; Olypher and Calabrese 2007; Ransdell et al. 2012; Swensen and Bean 2005). This poses the question of how these neurons can generate consistent activity patterns despite the variability of the current they express. It has been proposed that neurons can express different ionic currents in a co-regulated manner, which would result in the appearance of correlated ionic currents, maximal conductances or their transcripts numbers in a population of identified (identical) neurons. This has been observed in a number of neuronal cell types in several invertebrate species (Khorkova and Golowasch 2007; MacLean et al. 2003; Ransdell et al. 2013; Schulz et al. 2007; Tobin et al. 2009). However, that has typically been assumed to be an invertebrate idiosyncrasy. Evidence of their existence in vertebrates is largely indirect or anecdotal (Amendola et al. 2012; McAnelly and Zakon 2000). Nevertheless, there is persuasive theoretical work that suggests feasible mechanisms that generate these correlations (O'Leary et al. 2013; O'Leary et al. 2014), and the potential functional role of ionic current correlations (Hudson and Prinz 2010; O'Leary and Marder 2016). There is also evidence that the expression of ionic current correlations is a highly regulated phenomenon (Khorkova and Golowasch 2007), suggesting that correlations play important roles in the long-term dynamics of neuronal activity, the regulation of the robustness of this activity, or both. Here we report that ionic current correlations are widely distributed in mammalian neurons, with significant correlations between $K^+$, leak and transient inward currents in adult mouse cholinergic basal forebrain and hippocampal granule cells. We also have evidence of long-term regulation of some of these current correlations, suggesting a highly dynamic but slowly evolving interaction between the currents and their potential functional role. We conclude that the existence of correlations between ionic currents is not an invertebrate phenomenon, but a ubiquitous one among neurons.

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**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.18/L4

**Topic:** D.07. Vision

**Title:** Physiology, morphology and biophysically-realistic computational models of the human epileptic hippocampus

**Authors: *A. BUCHIN**[1], R. DE FRATES[1], P. CHONG[1], C. S. GERARD[2], B. E. KALMBACH[1], S. MCCONOUGHEY[1], U. RUTISHAUSER[3,4], R. GWINN[2], S. A. SORENSEN[1], J. T. TING[1], C. A. ANASTASSIOU[1,5]

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**Abstract:** Epilepsy is the fourth most common neurological disorder, and is responsible for a greater total global burden of disease than any neurological condition except stroke or migraine. Despite considerable advances in the treatment and diagnosis of seizure disorders, our understanding of the cellular and molecular mechanisms by which epilepsy develops (epileptogenesis) remains incomplete. To elucidate mechanisms underlying epileptogenesis in humans we study the excitability of human hippocampal neurons and networks in tissue slices from specimens excised during brain surgery for the treatment of focal, pharmacoresistant epilepsy. Specifically, we characterize electrophysiological and morphological features of single neurons via whole-cell patch clamping and reconstructed biocytin-fillings as a function of cell type for different hippocampal subfields. Importantly, these measurements are performed in ex vivo hippocampal slices derived from patients with varying degrees of hippocampal sclerosis (Watson grade 1-4). A major aim of this work is to bridge the spatiotemporal scales and causally link how changes at the component level (synapses, single-neuron excitability, etc.) are reflected at the network and the observable level (such as depth LFP, EEG, ECoG, etc.) To integrate these different facets, detailed biophysical single-neuron models are developed that account for observed ephys and morphology features as well as pathology-related alterations [Druckmann et al, Front Neurosci 2007; Reimann, Anastassiou et al, Neuron, 2013]. Ultimately, these computational simulations seek to bridge the gap between single-neuron biophysics, ensemble activity and experimentally recorded signals such as the depth EEG and multi-unit activity typically measured during seizures in humans. Using experiments and computational modeling we investigate the underlying causes of seizure disorders. In particular we investigate the hypothesis of epileptogenesis in the setting of hippocampal sclerosis (i.e. with varying degrees of morphological changes) in the dentate gyrus.

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**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.19/L5

**Topic:** B.09. Physiological Properties of Neurons

**Support:** The College of Medicine, University of Arkansas for Medical Sciences (startup funding to S.-H.L.)

NIH Grant P30 GM110702

**Title:** Cell type-specific intrinsic theta and gamma oscillations in hippocampal GABAergic interneurons

**Authors: *Y.-J. KANG**[1], G. GOVINDAIAH[1], H. E. SMASHEY[1], M. W. YOUNG[1], L. J. GREENFIELD, Jr.[1,3], E. GARCIA-RILL[2], S.-H. LEE[1]
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**Abstract:** The hippocampus plays a critical role in learning and memory, as well as in spatial processing, which are supported by coordinated network activity, including theta and gamma oscillations. Recent evidence suggests that hippocampal subregions (e.g., CA1) can generate these oscillations at the network level, at least in part through GABAergic interneurons. However, it is unclear whether specific GABAergic interneurons generate intrinsic theta and/or gamma oscillations at the single cell level. Since major types of CA1 interneurons (i.e., parvalbumin-expressing basket cells (PVBCs), cannabinoid type 1 receptor-expressing basket cells (CB1BCs), and neurogliaform family cells) are thought to play key roles in hippocampal oscillations, we tested the hypothesis that they generate intrinsic oscillations at the single cell level. We performed whole-cell patch-clamp recordings of GABAergic interneurons in the CA1 region of the mouse hippocampus in the presence of excitatory and inhibitory synaptic blockers to identify spontaneous intrinsic membrane potential oscillations. The majority of PVBCs (81%), but not the other interneuronal subtypes, produced intrinsic gamma oscillations if the membrane potential remained above -45 mV. By contrast, both CB1BCs and neurogliaform family cells, as well as the remaining PVBCs (19%) produced intrinsic theta/alpha, but not gamma, oscillations. These oscillations were blocked by persistent sodium current blockers (i.e., tetrodotoxin or riluzole). These data demonstrate that the three major types of hippocampal interneurons produce distinct frequency bands of intrinsic membrane oscillations. These findings support the possibility that intrinsic oscillatory properties of these interneuronal subtypes are key mechanisms of hippocampal theta and gamma oscillations at the network level, and suggest that specific interneuronal subtypes play different functional roles in hippocampal information processing. This work was supported by the College of Medicine, University of Arkansas for Medical Sciences (startup funding to S.-H.L.), and a Center for Translational Neuroscience award from the IDeA program at NIGMS, P30 GM110702.

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**Poster**

**474. Hippocampal and Entorhinal Neuronal Activity and Firing Properties**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 474.20/L6

**Topic:** B.09. Physiological Properties of Neurons

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**Title:** Influence of non-spatial information on spatial information in hippocampal granule cell

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**Abstract:** It was reported that spatial (place) and non-spatial (odor) information are integrated at hippocampal dentate gyrus in the brain. The dentate gyrus is a gate for memory association among cortexes. The granule cells (GCs) in hippocampal dentate gyrus receives two inputs from entorhinal cortex. Spatial information is delivered from medial entorhinal cortex to the medial dendrite (MD) through the medial perforant path (MPP). On the other hand, non-spatial information is delivered from lateral entorhinal cortex to the distal dendrite (DD) through the lateral perforant path (LPP). In addition, it was reported that 4-8Hz (theta rhythms) and 20-40Hz (gamma rhythms) oscillations were observed in the MPP and LPP in the rat brain during the odor discrimination task, respectively.To investigate the interaction of those two inputs, the frequency responses of GCs for the input with spatial information and non-spatial information were measured at 10-40 Hz of input frequency in rat hippocampal slices. During experiments, NMDA-receptors antagonist D-APV was applied to prevent from inducing the synaptic plasticity by frequency stimuli. In addition, inhibitory inputs were blocked by picrotoxin, GABAergic receptor antagonist. As the experimental result, GCs responses for successive inputs on DD sustained, suggesting a rate coding, and that 1md on is transient, suggesting a temporal coding.In addition, Multi-compartment GC with dynamic synapses model (Tsodkys et al. 1988) was developed using NEURON simulator and the model was fixed by parameter fitting for the physiological data. Regular burst inputs and random pulses were applied to MD and DD synapses, respectively. As the computational experimental result, the sensitivity for burst inputs to MD alone did not show a clear temporal pattern. In addition, as 20 Hz random pulses were simultaneously applied to DD, the GC activity was facilitated and the high temporal pattern sensitivity was observed. Moreover, as random pulse inputs were simultaneously applied to DD at 30-50 Hz, the GC activity was more facilitated. So that, the pattern discrimination was broad. Our results suggest that around 20Hz of DD inputs is suitable to enhance and tune the temporal-pattern of burst inputs to MD.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.01/L7

**Topic:** B.13. Demyelinating Disorders

**Support:** PML Consortium

Adelson Medical Research Foundation

**Title:** JC virus propagation is potentiated by glial replication & is accelerated by demyelination-associated glial proliferation

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**Abstract:** Progressive multifocal leukoencephalopathy (PML) is a devastating demyelinating infection in the central nervous system (CNS) of immunosuppressed individuals, mediated by the gliotropic polyomavirus JCV. We recently found that JCV replicated primarily in mitotic human glial progenitors and astrocytes, with oligodendrocyte death occurring through T antigen-mediated apoptosis rather than lysis. This observation raised the possibility that JCV infection might be potentiated by astrocytic replication, and hence accelerated in the setting of mitotic gliogenesis. To test this hypothesis, we first tagged dividing human astrocytes in vitro with bromodeoxyuridine (BrdU), then infected them with JCV MAD1 and confirmed that proliferating human astrocytes were more supportive for JC viral propagation, as early T antigen expression appeared both in $BrdU^+$ and $BrdU^-$ host cells, but the late VP1 antigen, whose expression indicates viral replication, only appeared in $BrdU^+$ cells at day 5 post-infection. Similarly, 5'-ethinyl 2'-deoxyuridine (EdU) labeling revealed more mitotic astrocytes among JCV-infected cells than among matched uninfected cells. In vitro scratch assays combining with MAD1 infection revealed that viral propagation was accelerated in the wound region, compared with regions distant to the scratch, tracking the increased glial proliferation rate in the wound area. On that basis, we next assessed the dependence of JCV infection upon local glial proliferation in vivo, using human glial chimeric mice subjected to cuprizone challenge. To this end, we established chimeras by engrafting human induced pluripotent stem cell (hiPSC)-derived glial progenitor cells (GPCs) into neonatal $rag1^{-/-}$ immune deficient C57B1/6 mice, and then injecting MAD1 JCV into the brains of these animals as adults, resulting in their active infection. The chimeras were then challenged with cuprizone diet (0.2% w/w, for 16w or 20w), which resulted in both demyelination and a proliferative response by the resident human glial cells.

Immunostaining for T antigen and VP1 revealed that JCV propagation was significantly accelerated in these mice. These results suggest that JCV propagation in PML may be potentiated by glial DNA replication, and that the accentuated glial cell division attending acute demyelination might provide an especially favorable environment for JCV propagation and hence PML progression. These data would argue for the aggressive prevention of new demyelinating events in patients at risk for PML. More broadly, this study expands our understanding on JC virus propagation and provides a model by which to further assess the pathogenesis and treatment of PML.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

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**Program#/Poster#:** 475.02/L8

**Topic:** B.13. Demyelinating Disorders

**Support:** Emerald Foundation

**Title:** A highly expanded IgA B-cell in the cerebrospinal fluid of a multiple sclerosis patient

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**Abstract: Introduction:** The effectiveness of B-cell targeted therapy in multiple sclerosis (MS) has rejuvenated interest in B-cells and the potential roles they may play in the pathogenesis of MS. MS B-cell interest has traditionally been due to the presence of cerebrospinal fluid (CSF) IgG oligoclonal bands, a diagnostic marker for MS. Recently, IgM antibodies have been reported as a potential indicator of clinical isolated syndrome conversion to MS and/or future disease severity. The association of IgA isotype B-cells or antibodies with MS however, has been lacking. We report here the presence of a highly expanded IgA isotype B-cell in the CSF of a clinically definite MS patient.
**Methods:** Twelve mL of CSF was obtained via lumbar puncture. Cells from CSF were centrifuged and stained for CD19 and CD138. Ninety six single cells were sorted via FACS for CD19 or CD138 positivity. Gene specific primers for immunoglobulin heavy and light chains were used for reverse transcription. Nested PCRs were performed to amplify the variable region and a small portion of the constant region. Sequencing yielded the variable region as well as identified the immunoglobulin isotype. ELISAs for protein levels were performed according to standard procedures.
**Results:** PCR and subsequent sequencing of the 96 single cell sorted CD19+ or CD138+ B-cells

yielded 67 heavy chain sequences with the following breakdown via isotypes: 40 IgA, 19 IgM, and 8 IgG. Variable region sequence analysis show 38 of the 40 IgA sequences shares identical CDR3 regions. This highly expanded IgA clone made up 56.7% of the sequenced identified CD19+ or CD138+ B-cells. The sequenced light chains also show this clonal expansion and also serve as a contamination check (identical CDR3 heavy chains also had identical CDR3 light chains). Albumin levels did not show blood brain barrier permeability out of normal range (CSF/Serum ratio of 3.8, normal at <9). CSF IgA levels was high at 7.7 µg/ml (normal at <2.3 µg/mL).
**Conclusion:** We report here an atypical MS CSF patient where the predominant B-cell detected in his CSF is a highly expanded CD19 or CD138 positive B-cell with an IgA isotype. Analysis using total amounts of CSF IgA as well as albumin levels in the CSF and serum is suggestive of intrathecal synthesis. Further research is being conducted to ascertain the specificity of this antibody and its relevance to disease pathogenesis.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

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**Program#/Poster#:** 475.03/L9

**Topic:** B.13. Demyelinating Disorders

**Support:** RG-1507-04951

**Title:** Evidence for neural-vascular uncoupling in multiple sclerosis: A calibrated functional MRI study in visual cortex

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**Abstract:** Multiple Sclerosis (MS) results in visual cortex (VC) dysfunction, even in the absence of ophthalmic pathologies. The precise mechanism of this dysfunction remains elusive. Our previous studies have shown an association between white-matter microstructure (WMMS) insult and reduced Blood-Oxygen-Level-Dependent (BOLD) signal in the VC of MS patients when compared to healthy controls. However, the physiological basis of the reduction in VC BOLD signal observed in MS remains unknown. We hypothesized that WMMS destruction affects communication between neurons and cerebral vasculature (ie., neurovascular coupling) and in turn, disrupts neural function. In this study, we sought to isolate the origin of MS-related

BOLD changes by comparing various components of the hemodynamic response function, blood-flow and oxygen metabolic constituents using dual-echo calibrated functional MRI (cfMRI). We conducted a case-control study comparing relapsing-remitting MS patients diagnosed by McDonald criteria with matched healthy controls. Participants were scanned using a 3T MRI scanner. We utilized a dual-echo pulse sequence that permitted near-simultaneous measurement of cerebral blood flow (CBF) and BOLD signal. In the scanner, participants performed a hypercapnia inhalation challenge while being scanned. They subsequently performed a block designed visual task. During the visual task, participants responded via bilateral button-press whenever a fixation cross at center-screen changed in luminance; during stimulation blocks, flickering checkerboards were presented at 6Hz.Individual data were preprocessed and convolved to obtain functional regions of interest (ROI). BOLD and CBF time series were obtained from these ROIs. Cerebral metabolic rate of utilization of oxygen ($CMRO_2$) was calculated using the deoxyhemoglobin dilution model. Whereas healthy controls exhibited stimulation-induced BOLD signal increases that were sustained across the block, MS patients exhibited stimulation-induced BOLD signal increases that declined across the block. Estimated maximum blood-oxygenation (the factor M) was higher in MS patients than healthy controls. During stimulation, increases in CBF and $CMRO_2$ were lower in MS patients than healthy controls. These results support the hypothesis that MS-related neural pathology arises more from neural and glial deficits than from vascular deficits and suggest that reduced neural metabolism plays a key role in MS-related reduction in neurovascular coupling.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** B.13. Demyelinating Disorders

**Support:** NMSS Grant RG150704951

**Title:** Progressive neural-vascular uncoupling with persistent motor activity in multiple sclerosis

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**Abstract:** Multiple Sclerosis (MS) leads to motor cortex (MC) dysfunction and this has been attributed to decreased alertness and fatigue. The neural-vascular coupling system, composed of cerebral blood vessels, glial cells, and neurons coherently function to maintain effective neural function. Previously, we have found reduced blood-oxygen-level dependent (BOLD) signal in the motor cortex of MS patients. However, the relative contributions of each neural-vascular component to reduced BOLD signal remain unknown. We performed a cross-sectional study comparing relapsing-remitting MS patients with healthy controls. All subjects who met the inclusion criteria were scanned using a 3T MRI scanner with a dual-echo calibrated functional MRI (cfMRI) sequence which provided near-simultaneous measures for both cerebral blood flow (CBF) and BOLD signal. During imaging, subjects performed a motor task which required bilateral button presses in time with a 2Hz auditory cue. An additional hypercapnia gas challenge involving inhalation of room air (4 min) and 5% $CO_2$ (6 min) permitted measures of cerebral metabolic rate of oxygen utilization ($CMRO_2$). Data were preprocessed and analyzed using the general linear model to obtain functional regions of interest (ROI). Percent signal change was obtained for each measure in these ROIs. During active blocks, MS patients displayed an initial rise in CBF followed by a gradual decline, whereas healthy controls exhibited a similar initial rise and a subsequent sustained plateau. CBF decreased in MS patients but BOLD signal was not different from healthy controls, suggesting lower $CMRO_2$ in MS patients. Estimated maximum blood-oxygenation (the factor M) was higher in MS patients than healthy controls. These results suggest progressive uncoupling between glial cells, neurons, and blood vessels with persistent stimulation of the motor cortex.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

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**Topic:** B.13. Demyelinating Disorders

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Dianne Cash Predoctoral Fellowship

**Title:** Relationships between hemodynamic response function canonicality and cognitive slowing in relapsing-remitting multiple sclerosis

**Authors: *M. P. TURNER**[1], N. A. HUBBARD[3], L. M. HIMES[1], D. K. SIVAKOLUNDU[2], J. HART, Jr.[1,4], D. T. OKUDA[4], E. FROHMAN[4], B. RYPMA[1,5]
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**Abstract:** The hemodynamic response function (HRF), a model of brain blood-flow changes in response to neural activity, arises from communication between neurons and the vasculature that supplies these neurons by means of glial cell intermediaries. Disruption of such communication might have consequences for cognition and performance. In demyelinating diseases, particularly Multiple Sclerosis (MS), white-matter microstructure is damaged, and performance is impaired. White-matter damage compromises the ability of neurons to adequately convey their metabolic needs, resulting in insufficient oxygen and nutrient perfusion. In this study, we isolated the components of the HRF that could quantify the extent to which damaged white matter affects neural-vascular coupling, and possibly cognitive symptoms experienced by MS sufferers. Twenty-eight relapsing-remitting MS patients and 23 healthy controls matched on age, sex, and education were scanned on a 3T MRI scanner (TE = 30 ms, TR = 2000 ms, 39 4-mm transverse slices, no gap, in-plane resolution 3.43 × 3.43 $mm^2$, 70$^o$ flip angle, 64 × 64 matrix). During scanning, participants performed (1) a simple button-press task, in which they responded via bilateral button-press whenever a flickering checkerboard appeared, and (2) an fMRI-adapted version of the WAIS Symbol Digit Modalities Task, in which they indicated via button-press whether a probe digit-symbol pair matched a corresponding pair in a key of 9 digit-symbol pairs. HRFs were modeled from visual, motor, and prefrontal brain regions during both tasks using piecewise linear-B spline functions, an approach that minimized assumptions regarding HRF shape that may not be valid for diseased populations. These functions were then characterized using several shape metrics. Group differences in peak amplitude (visual $p < 0.02$, motor $p < 0.04$, prefrontal $p < 0.01$), time-to-peak (prefrontal $p < 0.02$), full-width-at-half-maximum (motor $p < 0.05$), and area-under-curve (prefrontal $p < 0.01$) indicated significantly different HRF shapes between controls and patients. Relationships between processing speed task performance and both time-to-peak ($p < 0.004$) and area-under-curve ($p < 0.001$) were also observed. These results support the hypothesis that dysfunction of the neural-vascular communication system disrupts the nutrient delivery vital to intact neural functioning. They also support the hypothesis that pathological alterations to white-matter microstructure underlie MS-related cognitive performance deficits.

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Commercial Interest or their Agents (e.g., speakers' bureaus); Acorda, Genzyme, TEVA Neuroscience. F. Consulting Fees (e.g., advisory boards); EMD Serono, Genentech, Genzyme, Novartis, TEVA Neuroscience. **E. Frohman:** F. Consulting Fees (e.g., advisory boards); Acorda, Genzyme, Novartis, TEVA Neuroscience. **B. Rypma:** None.

**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.06/M2

**Topic:** B.13. Demyelinating Disorders

**Support:** Center for Multiple Sclerosis and Autoimmune Neurology at Mayo Clinic

Don and Fran Herdrich

**Title:** Restoring vision in a mouse model of optic nerve demyelination through transplantation of iPSC-derived oligodendrocyte precursor cells

**Authors: *M. M. STANDIFORD**[1], K. MIRCHIA[2], E. TRIPLET[2], C. L. HOWE[2]
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**Abstract:** In the United States, more than 400,000 people suffer from multiple sclerosis (MS). Often the first symptom patients will experience is optic neuritis. Optic neuritis is acute inflammation of the optic nerve and is associated with pain, temporary loss of vision, and chronic demyelination. Nearly 80% of MS patients will experience optic neuritis over the course of the disease and even patients without a clinical history of optic neuritis exhibit poor visual function. In order to restore visual function in these patients, the optic nerve axons must be protected and the myelin sheath repaired in order to reestablish high-speed, coordinated conduction of impulses. While there are a number of immunomodulatory therapeutics available, no therapies are currently approved for remyelination. Unlike the rest of the central nervous system, the optic nerve is uniquely accessible for drug delivery or cell transplantation using current clinical practices. Because the remyelinating capacity of endogenous oligodendrocyte precursor cells (OPCs) diminishes overtime in MS patients, we aimed to determine if transplantation of OPCs was a viable remyelination therapy in the optic nerve. We transplanted OPCs derived from induced pluripotent stem cells (iPSC) via intravitreal injection into our novel cuprizone-induced mouse model of optic nerve demyelination. These chronically demyelinated mice show both histological aberrations and visual defects. We find that following OPC transplant mice exhibit restoration of histological abnormalities and functional recovery as measured by normalization of visual evoked potentials. Herein, we show that transplantation of OPCs into the optic nerve is a viable therapeutic strategy for optic nerve demyelination.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.07/M3

**Topic:** B.13. Demyelinating Disorders

**Support:** A Cure for Ellie

**Title:** Conditional knockout of DARS2 results in white matter atrophy and neurobehavioral changes in mice

**Authors: *C. L. NEMETH**[1,2], S. N. TOMLINSON[1], C. F. MURRAY[1], C. TIFFANY[1], M. V. JOHNSTON[1,2], A. TRIFUNOVIC[3], A. FATEMI[2]
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**Abstract:** Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) is caused by mutations in DARS2, a gene encoding the mitochondrial enzyme aspartyl-tRNA synthetase. LBSL results in a rare, progressive, neurological disease that manifests as white matter signal abnormalities in the cerebral white matter and spinal cord, as well as slowly progressive dorsal column spasticity, dysarthria, and ataxia. To date, no animal model recapitulates disease pathology and no treatment exists. Previous attempts to develop an animal model of LBSL through the complete or conditional neuronal knock-out of Dars2 have been unsuccessful. Here, to mimic the clinical presentation in white matter, we developed a conditional knock-out of DARS2 using Cre-lox recombination in PDGFRα-expressing oligodendrocyte precursors. PDGFR$\alpha^{Cre+}$;Dars2$^{fl/fl}$ animals show a slight progressive behavioral phenotype with a reduction in both locomotor activity and rearing in open field over time, consistent with slowly progressive ataxia seen in LBSL. Preliminary data from these animals also suggests a reduction in oligodendrocyte transcription factor (Olig2)-expressing cells per area in the corpus callosum and an overall reduction in corpus callosum area relative to age-matched control littermates, consistent with white matter abnormalities observed in the clinic. This novel mouse model has the potential to elucidate mechanisms of LBSL and may allow for translation to clinical discoveries for the treatment of LBSL.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

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NMSS RG4958

The Mayo Clinic Center for Regenerative Medicine

**Title:** Targeting protease activated receptor 1 improves CNS myelin regeneration

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**Abstract:** Protease activated receptors (PARs) are a unique G-protein coupled receptor (GPCR) family, being activated by proteolytic cleavage within their extracellular domain to reveal a new amino-terminus that binds to the second extracellular loop to elicit intracellular signaling. PAR activating enzymes are known to be present in the intact central nervous system (CNS) and can also be elevated upon extravasation or after secretion by infiltrating immune cells in cases of neurological injury and disease. Despite this knowledge, little is currently understood regarding the consequences of CNS PAR activation or whether these receptors can be targeted to promote repair. Previous research in our laboratory has shown that several secreted serine proteases are highly enriched in white matter of individuals with demyelinating conditions, such as multiple sclerosis, or after spinal cord injury. In addition, we recently reported that PAR1 exhibits peak expression levels in the murine spinal cord at birth and that genetic deletion of PAR1 results in an accelerated pattern of spinal cord myelination, including higher levels of proteolipid protein at term and MBP levels in adulthood (Yoon et al., 2015). Collectively these data suggested that PAR1 is a key regulator of myelination and here we tested the hypothesis that PAR1 also regulates the process of remyelination. This hypothesis was investigated by determining whether genetic deletion of PAR1 impacts myelin regeneration in the lysolecithin model of focal demyelination. We accomplished this by systematic quantification of the amount of remyelination, astrogliosis, and inflammation in the spinal cord of adult male wild type or PAR1 knockout mice at 14 or 30 days after lysolecithin injection. PAR1 knockout mice showed improvements in the number of remyelinated axons compared to their wild type littermates 14 days after lysolecithin-mediated demyelination. Enhancements in myelin regeneration were

paralleled by increased numbers of both Olig2 and CC-1 positive oligodendrocytes and decreased numbers of Isolectin B positive microglia/monocytes at sites of myelin repair. These findings suggest that PAR1 is an essential rheostat of myelin generation and regeneration, such that inhibition of PAR1 may be a useful target to accelerate myelin repair in the adult CNS.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

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**Program#/Poster#:** 475.09/M5

**Topic:** B.13. Demyelinating Disorders

**Title:** Reduced myelin sheath thickness in aged forebrain-specific CTGF knockout mice

**Authors: *H.-C. CHANG**[1], L.-J. LEE[1,2,3]
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**Abstract:** In the nervous system, connective tissue growth factor (CTGF) is expressed in the cortical subplate, but its function is still unclear. In order to clarify the role of CTGF in the subplate, forebrain-specific *Ctgf* knockout (Fb*Ctgf* KO) mice were generated. In the present study, we characterized the phenotypes of aged mutant mice. Twenty one months old Fb*Ctgf* KO mice have equivalent weight and locomotor activity compared with age-matched control mice. In a series of behavioral tests, both control and Fb*Ctgf* KO mice showed similar emotion performances in open field test, elevated plus maze test and forced swimming test. In learning and memory tests, no significant difference was observed between control and Fb*Ctgf* KO mice in novel object recognition test and Y-maze test. It has been report that CTGF takes part in the maturation of oligodendrocytes and myelin formation, but whether CTGF participate in the maintenance of myelin structure is unknown. In the cerebral cortex, the expression of myelin basic protein was not altered in Fb*Ctgf* KO mice while the number of mature oligodendrocyte in white matters was also not changed. However, the thickness of myelin sheath in Fb*Ctgf* KO mice was thinner than control mice, whereas the axonal diameter was comparable between controls and mutants. Our results suggest a role of subplate-derived CTGF in the maintenance of myelin structure.

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**Poster**

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**Topic:** B.13. Demyelinating Disorders

**Support:** NIH Grant DK095911

**Title:** Modulating molecular chaperones improves demyelinating neuropathy in the MPZ-RAF mouse model

**Authors: *X. ZHANG**[1], B. S. J. BLAGG[2], R. T. DOBROWSKY[1]
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**Abstract:** Demyelinating neuropathies result from Schwann cell (SC) dedifferentiation upon loss of axonal contact or injury. Recent evidence suggests that c-jun is critical in promoting Schwann cell dedifferentiation. Elevated c-jun levels have been detected in a variety of human neuropathies suggesting that it may be a potential target for preventing or slowing the demyelination process. We previously demonstrated that modulation of heat shock protein 90 (Hsp90) with a small molecule Hsp90 modulator called KU-32 decreased c-jun expression and prevented demyelination in SC-neuronal co-cultures in a heat shock protein 70 (Hsp70)-dependent manner. In the current study, we utilized a transgenic mouse model (MPZ-Raf) in which injection of tamoxifen (TMX) leads to activation of the Raf-MAPK kinase pathway specifically in SCs. Elevated SC MAPK activity increased c-jun expression, demyelination and subsequent motor dysfunction. With this model, we sought to determine whether modulating heat shock proteins with KU-596, a third generation Hsp90 modulator, is sufficient to ameliorate the motor neuropathy that develops in these mice. Treating MPZ-Raf mice with KU-596 reduced the induction of c-jun but had no effect on the extent of MAPK activity. Drug treatment improved motor performance, delayed the onset of rear-limb paresis and ameliorated the extent of peripheral nerve demyelination in both prevention and intervention studies. Hsp70 was necessary for the neuroprotective efficacy of KU-596 since MPZ-Raf×Hsp70KO mice did not respond to KU-596 treatment. KU-596 is currently in Phase 1 clinical trials and our data indicate that modulating heat shock proteins may provide a novel therapeutic approach to attenuate c-jun induced demyelinating neuropathies in humans.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.11/M7

**Topic:** B.13. Demyelinating Disorders

**Support:** CIHR

MS society of Canada

**Title:** Lipid biochemistry probed with Nile Red spectral microscopy reveals novel features during cuprizone demyelination and remyelination

**Authors: *W. TEO**[1], A. V. CAPRARIELLO[2], M. MORGAN[1], P. K. STYS[3]
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**Abstract:** Myelin is a lipid-rich spiral wrapping of axons that facilitates rapid saltatory conduction. Although myelin is predominantly lipid (70-85% w/w), a lack of methods for studying lipids in tissue sections has hindered our understanding of changes in intact and pathological myelin. Using the solvatochromic lipophilic fluorescent dye Nile Red (NR), whose fluorescence spectral profiles change with biochemical alterations in the local tissue environment, we report a number of novel tissue defects in the cuprizone (CPZ) animal model of de/re-myelination, particularly at early time points, below the threshold for detection by conventional methods. After only a single week of CPZ treatment, well before overt demyelination, lipids in the corpus callosum (CC) exhibited distinct biochemical changes, preceding overt demyelination. Accumulation of intense lipid droplets between the lateral CC and hippocampal white matter provided further evidence of early lipid pathology. At 2 weeks of CPZ, a time point also lacking overt histological defects, active myelin change reported by NR spectral shifts around the lateral ventricles was seen together with lipid droplet accumulation. Further, focal lesions of lipid loss were identified in grey and white matter, with no correlates by standard immunohistochemistry (MBP, IBA-1), suggesting that NR lipid histochemistry was more sensitive to early pathological changes than conventional protein immunohistochemistry. At week 3 of CPZ, when demyelination is known to occur, lipids continued to exhibit even more abnormal signatures with further accumulation of lipid droplets in demyelinated areas. After 6 weeks of CPZ + 4 weeks recovery, re-myelination was robust but NR showed that regenerated myelin was biochemically abnormal, exhibiting features of early 1 week CPZ signatures. CONCLUSION: solvatochromic properties of NR coupled with spectral microscopy represent a powerful new tool for detecting very early and subtle myelin damage, likely reflecting lipid biochemical changes. This method is more sensitive than conventional techniques such as myelin stains and immunohistochemistry. Furthermore, NR microscopy suggests that remyelination, at

least in the CPZ model, is aberrant, which may have implications for delayed degeneration which has been reported in this model.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.12/M8

**Topic:** B.13. Demyelinating Disorders

**Support:** United Leukodystrophy Foundation

Juanma Fund

**Title:** Antisense oligonucleotide therapy elicits rapid, sustained pathology reversal in a mouse model of Alexander disease

**Authors: *B. POWERS**[1], T. HAGEMANN[2], C. MAZUR[1], E. SWAYZE[1], A. MESSING[2]
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**Abstract:** Alexander disease (AxD) is a fatal leukodystrophy caused by autosomal dominant missense mutations in the gene for glial fibrillary acidic protein (GFAP). Mutations cause GFAP to accumulate above a toxic threshold and aggregate with other proteins into intra-astrocytic inclusions called Rosenthal fibers (RFs), the pathological hallmark of the disease. Seizures, megalocephaly and developmental delay occur in early-onset patients, while late-onset patients instead exhibit bulbar signs, spasticity, and ataxia. AxD knock-in mice carry point mutations in mouse *Gfap* that are orthologous to patient mutations and exhibit spontaneous, pronounced GFAP overexpression and RFs. We investigated the therapeutic potential of antisense oligonucleotides (ASOs) to reduce mouse GFAP expression and reverse disease pathology in knock-in mice. We administered a single intracerebroventricular (ICV) bolus injection of an ASO targeting GFAP in 8 week old mice that exhibit marked GFAP overexpression and RF burden. We observed up to 99% GFAP mRNA reduction in the CNS one week post-ICV. GFAP protein was reduced to WT levels by 4 weeks post-ICV and continued to decline between 4-8 weeks. RF burden was reduced 2 weeks post-ICV and completely reversed by 4 weeks after ASO administration. Markers of microglial activation/recruitment (Aif1 mRNA) and oxidative stress (Nqo1 mRNA) markedly declined to nearly WT levels by 1 and 2 weeks post-ICV, respectively. GFAP suppression and complete pathology reversal continued out to 16 weeks. In conclusion, ASOs targeting GFAP show great promise as a therapeutic strategy to achieve rapid and sustained reversal of AxD pathology.

**Disclosures:** **B. Powers:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ionis Pharmaceuticals. **T. Hagemann:** None. **C. Mazur:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ionis Pharmaceuticals. **E. Swayze:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ionis Pharmaceuticals. **A. Messing:** None.

**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.13/M9

**Topic:** B.13. Demyelinating Disorders

**Support:** TerCell

Ciberned

SAF-2016-79774-R

**Title:** IL-37 exerts therapeutic effects in experimental autoimmune encephalomyelitis

**Authors: *A. SÁNCHEZ FERNÁNDEZ**[1], C. DINARELLO[2,3], R. LÓPEZ-VALES[1]
[1]Cell Biology, Immunol. and Physiol., Univ. Autonoma De Barcelona, Bellaterra, Spain; [2]Div. of Infectious Dis., Univ. of Colorado Denver, Aurora, CO; [3]Dept. of Med., Radboud Univ. Med. Ctr., Nijmegen, Netherlands

**Abstract:** Multiple sclerosis (MS) is a chronic, autoimmune and degenerative disorder that causes central nervous system demyelination and axonal injury. MS affects 2.5 million people worldwide and it is highly disabling. Although its ethology remains elusive, several lines of evidence support the concept that autoimmunity plays the major role in disease pathogenesis. The current treatments for MS are unable to prevent disease progression. Interleukin 37 (IL-37), one of the eleven members of the IL-1 family, is known to broadly reduce innate inflammation as well as acquired immunity. IL-37 has demonstrated to mediate significant resistance against several inflammatory challenges, including after spinal cord injury. Thus, based on its protective and anti-inflammatory properties, we hypothesized that IL-37 could mitigate the neurological deficits in MS.
Since IL-37 is not present in the mouse, in the present study, we induced experimental autoimmune encephalomyelitis (EAE) in transgenic mice expressing the human form of IL-37

(hIL-37tg) or in wildtype littermates. Mice were immunized subcutaneously with myelin oligodendrocyte glycoprotein 35-55 peptide emulsified in complete Freund's adjuvant containing *Mycobacterium tuberculosis.* Immediately after the immunization and 48h later, mice were intraperitoneally injected with pertussis toxin.
We firstly assessed the changes in mRNA levels of IL-37 during the course of the disease. Real time PCR experiments revealed that IL-37 transcripts were barely detected in the spinal cord of unimmunized and immunized mice at the onset of EAE. However, strong induction of IL-37 (~7 fold increased) was observed at the peak and progression phase of the disease. We then evaluated whether IL-37 attenuated the clinical signs of the disease. We found that transgenic expression of IL-37 did not delay the onset of the disease, but markedly reduced neurological deficits. Moreover, histological analysis revealed that IL-37 conferred protection against myelin loss. Taking together, this study presents novel data indicating that IL-37 may have therapeutic potential for the treatment of MS.

**Disclosures: A. Sánchez Fernández:** None. **C. Dinarello:** None. **R. López-Vales:** None.

**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.14/M10

**Topic:** B.13. Demyelinating Disorders

**Support:** NSFC/RGC N_HKU741/11

SK Yee Medical Research Fund

HKU Strategic Research Theme

**Title:** *In vitro* derivation of oligodendrocyte precursors from neural progenitors harbored in the adult bone marrow - implications for remyelination therapy

**Authors: *D. K.-Y. SHUM**, Y. P. TSUI, K. L. K. WU, Y. S. CHAN
Sch. of Biomedic. Sci., Fac. Med., Univ. Hong Kong, Hong Kong, China

**Abstract:** Loss of myelin due either to congenital abnormalities or traumatic injuries impacts on conduction of nerve impulses, causing neurological deficits. Our recent success with a strategy that enriches and expands the neural progenitor subpopulation among adult samples of bone marrow stromal cells provided impetus for pursuit of bone marrow-derived neural progenitors (BM-NPs) as source for deriving oligodendrocyte precursors (OPs) for use in transplantation and remyelination. Cultures of rat BM-NPs treated with supplements of β-heregulin, PDGF-AA and bFGF fostered the derivation of oligodendrocyte precursors in 3 weeks. These BM-OPs were positive for the OP markers, NG2, Olig2, PDGFRα and Sox10. The BM-OPs were then

subjected to *in vitro* myelination assay in co-cultures with purified DRG neurons. In 2 weeks, BM-OPs matured into oligodendrocytes and extended myelin basic protein-positive processes along multiple neurites. The BM-OPs were further transplanted into the corpus callosum of myelin-deficient, juvenile Shiverer mice. Mature oligodendrocytes and ultrastructure of compact myelin were identifiable in the corpus callosum in 6 weeks. Our findings indicate BMSCs as a possible source of oligodendrocyte precursors for CNS remyelination therapy.

**Disclosures: D.K. Shum:** None. **Y.P. Tsui:** None. **K.L.K. Wu:** None. **Y.S. Chan:** None.

**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.15/N1

**Topic:** B.13. Demyelinating Disorders

**Support:** The Paul K. and Anna E. Shockey Family Foundation

**Title:** Serum enkephalin levels correspond to disease severity in EAE

**Authors: *P. J. MCLAUGHLIN**, M. D. LUDWIG, I. S. ZAGON
Dept Neural & Behav Sci., Penn State Univ. Coll Med., Hershey, PA

**Abstract:** Experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis presents with increased levels of cellular proliferation within the immune system (T and B lymphocytes) and central nervous system (astrocytes and glia). Opioid growth factor (OGF), is an endogenous opioid chemically termed [$Met^5$]-enkephalin. Systemic injections of OGF in models of chronic progressive EAE or relapsing-remitting EAE beginning either at the time of immunization or following established disease have demonstrated substantial reductions in clinical disease, relapses, and numbers of activated astrocytes, glial/macrophages, and demyelination. In this study, serum OGF levels were monitored throughout the course of progressive EAE and correlated to clinical behavior, activity in an open field, and sensitivity. C57Bl/6J mice were immunized with myelin-oligodendrocytic glycoprotein and treated daily with either OGF or saline. Clinical behavior was monitored daily, and locomotor activity and thermal sensitivity were measured periodically. Blood samples were collected periodically and enkephalin (OGF) levels measured by ELISA (MyBiosource). Peak disease scores for saline-injected EAE mice reached a mean of 5.7 (scale 1-10) on day 18, in comparison to a peak clinical score of 2.5 for OGF-treated EAE-mice. Serum OGF levels in EAE mice between 8 and 128 pg/ml over the course of disease in comparison to normal, non-diseased mice with stable OGF levels averaging 149 pg/ml. Exogenous OGF therapy increased serum levels in EAE mice corresponding to markedly reduced disease severity, increased open field behavior and decreased hot-plate sensitivity. These data suggest that there is a dysregulation of endogenous OGF in the

disease state and that treatment with exogenous OGF restores serum enkephalins to normal. Thus, the relatively non-invasive measure of serum OGF may be a useful marker for disease progression and therapeutic response.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.16/N2

**Topic:** B.13. Demyelinating Disorders

**Support:** Board of Directors, Tisch MS research center of NY

**Title:** Methionine metabolism is altered in multiple sclerosis

**Authors: *F. MIR**[1], Z. BALIC[2], J. JIAN[1], S. A. SADIQ[1]
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**Abstract:** Methionine is an essential amino acid which is critical for a number of metabolic processes such as protein synthesis, methylation, sulfur metabolism, redox regulation, and signal transduction. Methionine is highly susceptible to oxidation in vivo and the principal product of methionine oxidation is methionine sulfoxide (MetSO). Proteins lose their biological activity when specific methionine residues are oxidized to MetSO. In the current study we investigated the involvement of methionine oxidation in the pathophysiology of multiple sclerosis (MS). Cerebrospinal fluid (CSF) was obtained from MS patients (n=120) and age- and sex-matched controls (n=30) with informed consent under an IRB-approved protocol. Methionine metabolites were quantified by mass spectrometry (AbsoluteIDQ p180, Biocrates, Austria). Methionine sulfoxide levels were found to more than two fold elevated in the CSF of MS patients as compared to the controls (p=0.017). Interestingly this increase in MetSO was more pronounced in the progressive MS patients (p=0.0003) and more modest in the relapsing remitting MS patients (p=0.02) as compared to the control population. The MetSO/Met ratio also increased in the MS cohort. These results were further confirmed by an ELISA using an anti- MetSO antibody in an independent cohort of MS patients. In a parallel study using experimental autoimmune encephalomyelitis (EAE), we found MetSO levels to be increased in the brain and spinal cord lysates of mice during disease peak. This was accompanied by a concomitant decrease in the methionine sulfoxide reductase levels. Taken together these results indicate a dysregulation of methionine metabolism during MS and may have effects on DNA methylation, myelin gene expression and anti-oxidant levels contributing to the pathophysiology of MS.

**Disclosures: F. Mir:** None. **Z. Balic:** None. **J. Jian:** None. **S.A. sadiq:** None.

**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

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**Program#/Poster#:** 475.17/N3

**Topic:** B.13. Demyelinating Disorders

**Support:** Brian's Hope

Run for ALD Foundation

NINDS RO1NS097511 02

**Title:** Evaluation of dendrimer-4phenylbutyrate in X-linked adrenoleukodystrophy patient derived cells

**Authors: C. L. NEMETH**[1], B. TURK[2], C. F. MURRAY[2], *C. TIFFANY[2], O. GOK[3], A. SHARMA[3], S. KAMBHAMPATI[3], R. RAMIREDDY[3], A. B. MOSER[2], P. A. WATKINS[2], R. M. KANNAN[3], S. KANNAN[4], A. FATEMI[5]
[1]KennedyKrieger Institute/Lipid Lab., Baltimore, MD; [2]Kennedy Krieger Inst., Baltimore, MD; [3]Ctr. for Nanomedicine at the Wilmer Eye Inst., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Anesthesiol. and Critical Care Med., [5]Neurol., Johns Hopkins Univ., Baltimore, MD

**Abstract:** X-linked adrenoleukodystrophy (X-ALD) is a neurodegenerative disorder due to defects in the peroxisomal membrane transporter protein, ABCD1, with variable phenotypes ranging from a rapidly progressive, inflammatory cerebral demyelination (cerebral ALD) in young boys and adult men to the chronic slowly progressive adult onset adrenomyeloneuropathy (AMN) affecting men and women. Hallmark pathophysiology includes accumulation of very long chain fatty acids (VLCFA), increased oxidative stress, and progressive axonopathy, with little to no genotype-phenotype correlation. Furthermore, X-ALD phenotypic variability complicates prognosis and treatment. Allogeneic hematopoietic cell transplantation is effective in early stages of cerebral ALD but not in other forms and no other effective interventions exist. Recent advancements in dendrimer nanoparticle therapeutics provide platforms in which dendrimer-drug conjugates enable targeted and intracellular slow release of drugs requiring fewer treatments at lower drug concentrations. One such drug, 4-Phenylbutyrate (4PBA) has been shown to increase expression of ABCD2 and proliferation of peroxisomes in models of X-ALD; however, with a half-life of less than one hour, 4PBA requires frequent high dosages, precluding its utility in the clinic. Previously, we have demonstrated specific uptake of PAMAM dendrimer-drug conjugates in spinal cord neurons of the ABCD1 knockout mouse as well as within patient-derived primary macrophages and fibroblasts. Here, we demonstrate efficacy of 4PBA conjugated to dendrimer in both of these cell types to significantly alter biochemical and inflammatory abnormalities. In macrophages derived from ALD and AMN patient peripheral

blood monocytes, a 6h stimulation of 30 μM VLCFA leads to significant release of TNF ($p$ = 0.009, compared to unstimulated cells) and pretreatment with D-4PBA prevents these increases (30 μM D-4PBA, $p$ = 0.0018; 100 μM D-4PBA, $p$ = 0.002; 300 μM D-4PBA, $p$ = 0.002). Furthermore, treatment with 3 or 10 μM D-4PBA increases enzyme activity of SOD1, an important anti-oxidant regulator of cell death ($p$ = 0.0142 and $p$ = 0.0174, respectively). Similarly, in another in vitro model of ALD and AMN patient derived fibroblasts, reductions of VLCFA (C26:0 and C26/C22) were detected after a 16-day exposure to 30 μM (AMN $p$ = 0.017) or 100 μM D-4PBA (ALD $p$ = 0.026; AMN $p$ = 0.0006). Together, these data support feasibility and efficacy of low dose and versatile nanoparticle therapy to reduce ALD-related disease burden in patient derived cells and sets the stage for new therapeutic opportunities for complex diseases such as X-ALD.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.18/N4

**Topic:** B.13. Demyelinating Disorders

**Support:** Emerald Foundation

**Title:** Cerebrospinal fluid IgA levels correlate with disease activity in patients with multiple sclerosis; A novel finding

**Authors: A. LIANG**, A. FINNEY-STABLE, J. LIN, *S. A. SADIQ
Tisch MS Res. Ctr., New York, NY

**Abstract: Background:** Cerebrospinal fluid (CSF) IgG oligoclonal bands is a diagnostic biomarker of multiple sclerosis (MS) and a majority of these patients have IgG indexes above normal range (N <0. 7), an indicator of intrathecal IgG production. Recent literature also suggests a presence of CSF IgMs in patients with more severe forms of MS. We have previously shown that CSF fetuin-A levels has been linked to inflammatory disease activity. To further elucidate the role of B-cells in MS and associated disease activity, we investigated the presence

of IgGs, IgMs, and IgAs, and tested for correlations with CSF fetuin-A levels.
**Methods:** In a continuing study, CSF and serum samples from 30 MS patients were analyzed by ELISA to calculate indexes for IgGs, IgMs, IgAs, and albumin. Testing for previously reported biomarkers of disease activity, CSF was further analyzed by ELISA for fetuin-A, and osteopontin. Significant correlations were determined by a non-parametric Spearman test using the statistical program GraphPad Prism.
**Results:** CSF fetuin-A levels significantly correlated with CSF IgAs ($r = 0.5755$, $p = 0.0009$). Further analyses showed that CSF fetuin-A levels also significantly correlated IgA index ($r = 0.4434$, $p = 0.0205$). No correlations were found with IgG indexes, IgM indexes, and osteopontin.
**Conclusion:** We have identified a subset of MS patients with high CSF IgA levels that has not been reported in previous literature. Further investigation is required to elucidate the role of IgAs in the B-cell response for MS. In addition, high CSF IgA levels were an indicator of intrathecal IgA production and does not support a presence of a blood brain barrier breakdown. Unlike IgGs and IgMs, IgAs appears to correlate with disease activity, as demonstrated with its positive correlation to CSF fetuin-A levels. Future studies should be performed to determine if intrathecal IgA production decreases post-treatment in MS patients.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.19/N5

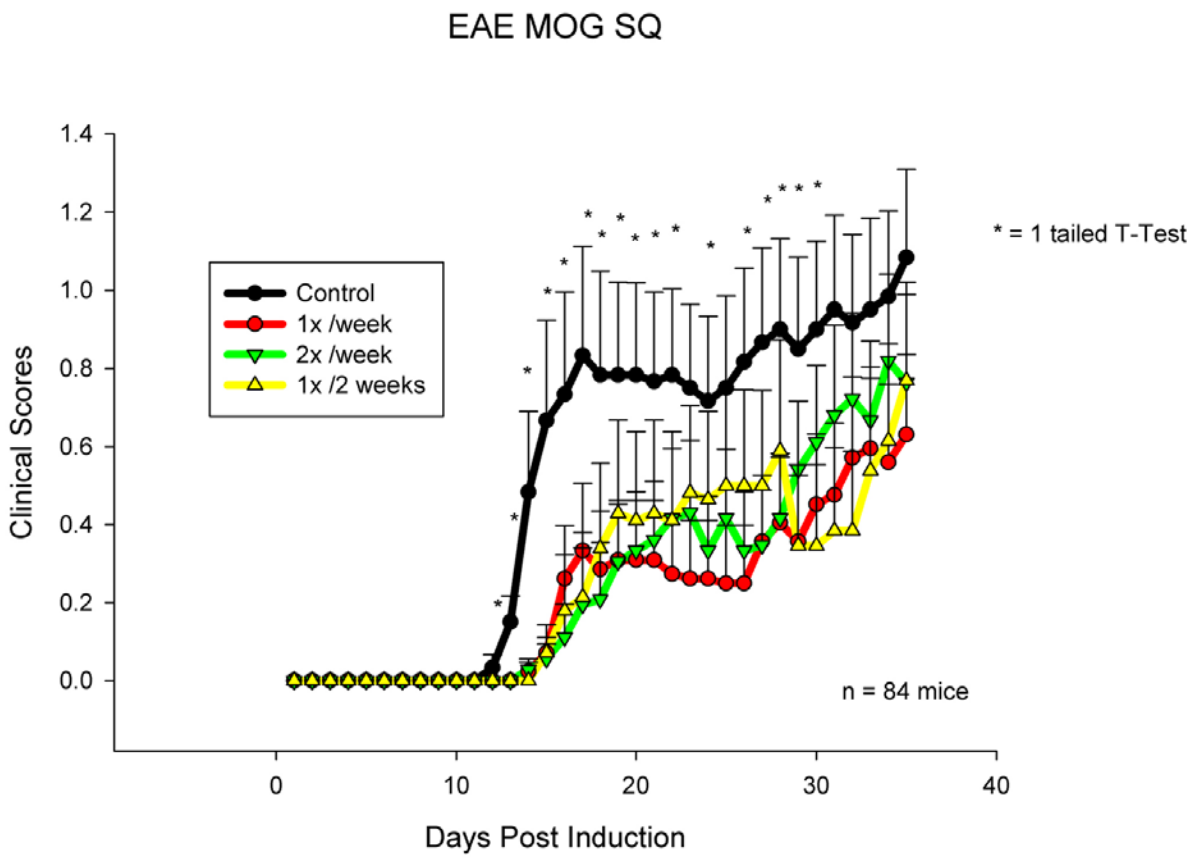
**Topic:** B.13. Demyelinating Disorders

**Title:** Treatment with cerium oxide nanoparticles in a mouse model of multiple sclerosis: Identifying the minimum effective subcutaneous dose

**Authors: B. R. BARNES**[1], W. E. DECOTEAU[2,3], J. E. BUCKLEITNER[2], T. A. BEDARD[2], S. C. HENEGAN[2], E. M. NEEDHAM[2], J. A. ROBINSON[2], M. M. GARDNER[3], *A. Y. ESTEVEZ[1], J. S. ERLICHMAN[2], K. L. HECKMAN[1]
[1]Biol., [2]Neurosci., [3]Psych., St. Lawrence Univ., Canton, NY

**Abstract:** Antioxidants are potential therapeutic agents for multiple sclerosis due to their ability to neutralize reactive oxygen species generated during pathogenesis, though this potential has not yet been convincingly translated to clinical use. Previously we have shown 2 nm cerium oxide nanoparticles (CeNPs) dampened the severity of experimental autoimmune encephalomyelitis (EAE) and improved motor function in EAE mice when delivered intravenously (ACS Nano 2013 7 (12), 10582-10596). Here we explore the efficacy of delivering CeNPs delivered subcutaneously in the murine EAE model. CeNP treatment began 7 days after disease induction,

a time when demyelination was underway. Doses ranging from 5-20 mg/kg/week significantly reduced clinical severity compared to controls. In addition, motor performance, assessed by hanging wire and rotarod, where also significantly improved in CeNP treated animals. A dose-dependent effect was apparent in the hanging wire task but not the rotarod or clinical severity suggesting that we were close to a ceiling effect with respect to biological activity at this dose regimen. These findings demonstrate that subcutaneously delivered CeNPs are effective at mitigating disease progression in the EAE model and that the minimum effective dosing will likely be lower than 5 mg/kg/week in this model.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.20/N6

**Topic:** B.13. Demyelinating Disorders

**Support:** NMSS Grant RG-1501-02876

**Title:** Adult oligodendrocytes can play a role in remyelination

**Authors: *I. D. DUNCAN**[1], L. A. WIERENGA[1], M. HEIDARI[1], A. B. RADCLIFF[1], G. KIDD[2]
[1]Dept Med. Sci., Univ. Wisconsin Sch. Vet Med., Madison, WI; [2]Renovo Neural, Inc., Cleveland, OH

**Abstract:** Remyelination of the CNS is the default pathway following demyelination in practically all myelin disorders. Remyelination is a prominent feature in multiple sclerosis, at least early in the disease, but eventually lessens and fails with time. To-date, the weight of evidence identifies the oligodendrocyte progenitor cell (OPC), which is found both in developing and mature white matter, as the source of remyelinating oligodendrocytes. In contrast, the adult oligodendrocyte (OL) is thought to be incapable of playing a role in remyelination, despite certain *in vitro* data that suggests that these cells may in fact be able to re-ensheath axons. We have explored this question using a novel model of demyelination and remyelination known as FIDID (feline irradiated diet induced demyelination). In this disorder, there is extensive vacuolation of myelin in the spinal cord that leads to scattered but frequent demyelination, with demyelinated axons adjacent to axons with surviving, mature myelin sheaths. At the same time, in these areas, thinly remyelinated axons are present. To explore the cellular milieu underlying this array of myelin changes, we first asked if OL cell death occurred as a cause of the demyelination. TUNEL labeling showed that there was little to no cell death and pyknotic cells were rarely seen on light microscopy or EM, hence adult OLs appear to survive and are adjacent to scattered demyelinated axons. We then identified individual OLs on EM and found cells that had processes extending both to mature and thin myelin sheaths. We interpret this finding as demonstrating that surviving OLs have processes to both mature and immature (thinly myelinated) internodes. Furthermore, we confirmed these observations by tracing the cell processes of single OLs using 3-D reconstruction (Renovo Neural, Inc.). We propose that in this model, the adult OL can play an important role in the remyelination, especially in the lateral and ventral columns of the spinal cord. The difference between the outcome here and those studies where the OPC is the ‘dominant’ cell, may be due to differences in the pathologic milieu. The data presented here however, suggest that the adult OL, perhaps surprisingly, may be a contributor to myelin repair in certain myelin disorders.

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**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.21/N7

**Topic:** B.13. Demyelinating Disorders

**Support:** Tisch MS Research Center of New York Private Funds

**Title:** Effects of intrathecal delivery of primary and secondary progressive MS cerebrospinal fluid on motor function and CNS pathology

**Authors: *J. K. WONG**, N. J. KUNG, S. A. SADIQ
Tisch MS Res. Ctr. of New York, New York, NY

**Abstract:** Multiple sclerosis (MS) is characterized by inflammatory demyelination, astrogliosis and axonal loss in the CNS. Most patients present with relapsing-remitting MS (RRMS) then eventually enter a phase of disease progression termed secondary progressive MS (SPMS). However, approximately 10-15% of patients have primary progressive multiple sclerosis (PPMS), which is characterized by unremitting disease progression from disease onset. Although PPMS and SPMS patients both experience continuous neurological decline, there are differences in their lesion distribution and extent of inflammation. It remains unclear whether the pathophysiological mechanisms contributing to clinical progression in PPMS and SPMS are the same.

Here, we investigated whether intrathecal delivery of cerebrospinal fluid (CSF) obtained from PPMS and SPMS patients would have similar effects on behavior and CNS pathology in mice. Mice underwent laminectomies at cervical levels 4 and 5 to expose the underlying spinal cord and CSF was injected under the dura mater into the subarachnoid space. Control animals were injected with saline or CSF from healthy donors. Functional deficits were assessed by evaluating forelimb reaching, gripping and tail rigidity at various time points following intrathecal CSF delivery. Mice injected with PPMS CSF displayed significantly higher behavioral deficit scores than control animals, as well as SPMS CSF-injected mice. Mice injected with SPMS CSF did not show functional impairments and scores were not statistically different from controls. Mice were perfused at 1 day post injection (DPI), 3 DPI, and 7 DPI. Brains and spinal cords were post-fixed overnight in 4% paraformaldehyde, cryoprotected in 30% sucrose, then cryosectioned for histological analyses. Spinal cords from mice injected with PPMS CSF exhibited evidence of astrogliosis at all time points, as revealed by significantly increased GFAP immunostaining in the dorsal white matter. However, astrogliosis was not observed in mice injected with SPMS CSF. Similarly, a significant increase in immunostaining intensity for SMI-32, a marker of

axonal damage, was observed in mice injected with PPMS CSF, but not SPMS CSF. In contrast, Iba1 immunostaining was similar in all groups, suggesting that microglia do not play a major role in contributing to deficits and pathology observed in PPMS CSF-injected mice. No group differences in GFAP and Iba1 immunostaining were observed in the corpus callosum and hippocampus, indicating that the effects of PPMS CSF remain localized at the site of delivery. The induction of behavioral deficits and spinal cord pathology appears to be unique to PPMS CSF, not SPMS CSF.

**Disclosures: J.K. Wong:** None. **N.J. Kung:** None. **S.A. Sadiq:** None.

**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.22/N8

**Topic:** B.13. Demyelinating Disorders

**Support:** NIH grant NS077215

**Title:** Drug screening for remyelination using a cerebral neural aggregate culture system

**Authors: *S. J. KIM**[1], H. KOI[1], D. MICHAUD[1], S. DONOVER[2], M. BITTNER[3], R. Q. LU[4], M. REICHMAN[2], J. LI[1]
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**Abstract:** Enhancing CNS remyelination represents an attractive therapeutic strategy for demyelinating diseases such as multiple sclerosis. As CNS myelination requires a myriad of cell interactions and communications, functional cell-based systems that recapitulate this process are necessary for screening non-neurotoxic small molecules that capable of promoting myelin repair. Here we describe a cerebral myelinating aggregate culture system that closely mimics *in vivo* myelination and retains axon-glial interactions and our results from screening 2460 pharmaceutical compounds. The neural aggregate culture system was generated from E15.5 mouse forebrains, composed primarily progenitors of neurons, astrocytes and oligodendrocytes, and were maintained in a serum-free medium for up to 4 weeks in Matrigel-coated 96-well plates. Radial growth of axons was robust after 1-2 days in culture (DIV) and extensive axonal networks were formed around 2 weeks *in vitro*. Glial progenitors migrated out of aggregates and gradually differentiated into astrocytes and axon-ensheathing oligodendrocytes, thereby establishing a 2.5D culture platform that provides suitable cellular environment for *in vivo* applicable drug screening. To develop quantitative high-throughput *in vitro* assays that enable

assessment of myelination and morphological changes of oligodendrocytes, we used an ImageXpress Micro XLS system to track oligodendrocyte differentiation over time in aggregate cultures prepared from transgenic mice expressing the membrane-anchored green fluorescent protein (mEGFP) under the promoter of 2′-3′-cyclic nucleotide 3′-phosphodiesterase (CNP1). CNP-mEGFP mice allowed us to visualize mature/myelinating cells and myelin along the axon. We identified multiple molecules that significantly enhance myelination and oligodendrocyte differentiation in the aggregate cultures and further validated the results using organotypic brain slices. After considering chemical structures, we chose 5 compounds that could permeate the blood brain barrier and tested their effects on remyelination using the lysolecithin-induced corpus callosum de/remyelination mouse model. We are currently analyzing the *in vivo* effects of the identified compounds on remyelination.

**Disclosures: S.J. Kim:** None. **H. Koi:** None. **D. Michaud:** None. **S. Donover:** None. **M. Bittner:** None. **R.Q. Lu:** None. **M. Reichman:** None. **J. Li:** None.

**Poster**

**475. Demyelinating Disorders: Mechanisms and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 475.23/N9

**Topic:** B.13. Demyelinating Disorders

**Support:** Mayo Clinic Center for MS and Autoimmune Neurology

Mayo Clinic Center for Regenerative Medicine

NMSS Grant FG-1607-25381

**Title:** Demyelination causes recruitment of axon-specific CD8+ T cells to the CNS leading to further injury

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**Abstract:** Clonally expanded CD8+ T cells outnumber their CD4+ counterparts in MS lesions yet their role in disease pathogenesis and the relevant target antigen(s) remain unknown. We posited that CNS CD8+ T cells are specific for neuronal antigen and may participate in axon or neuron injury in multiple sclerosis—thereby contributing to cumulative disability. We have previously shown in a viral mouse model of multiple sclerosis that perforin-competent CD8+ T cells are necessary and sufficient to cause axon injury in the context of overt demyelination. Furthermore, we showed that in vitro OT-1 T cells can cause perforin-dependent axon injury to neurons presenting the immunodominant SIINFEKL epitope in the context of MHC class I following treatment with interferon gamma. Here we further demonstrate that in addition to

interferon gamma treatment, demyelination is sufficient to drive neuronal expression of MHC class I genes as well as antigen processing genes, leading to recruitment of activated CD8+ T cells that are specific for axonally targeted neo-antigens, and that these CNS-recruited CD8+ T cells contribute to elimination of antigen-expressing axons. These findings support a role for autoreactive CD8+ T cells in the axonal injury that underlies progression in multiple sclerosis. Future studies are aimed at identifying patients with pathogenic anti-axonal CD8+ T cells who may be responsive to targeted immunotherapy.

**Disclosures: B. Clarkson:** None. **K. Mirchia:** None. **M.M. Standiford:** None. **C.L. Howe:** None.

**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.01/N10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** BrightFocus

**Title:** Peripherally-expressed apoE isoforms differentially affect brain functions

**Authors: *C.-C. LIU**, Y. CHEN, N. ZHAO, W. QIAO, N. WANG, J. ROGERS, J. ZHAO, C. M. LINARES, J. KNIGHT, A. KURTI, J. FRYER, B. KIM, G. BU
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**Abstract:** Alzheimer’s disease (AD) is the leading cause of dementia in the elderly with currently no disease-altering therapy. The ε4 allele of the apolipoprotein E (*APOE*) gene is the strongest genetic risk factor for late-onset AD among its three polymorphic alleles (ε2, ε3 and ε4). ApoE4 promotes Aβ aggregation and deposition and is associated with impaired brain lipid homeostasis, glucose metabolism, vascular functions and increased neuroinflammation. Thus, understanding the pathobiology of apoE4 represents a great opportunity to both uncover mechanisms underlying AD risk and also explore new strategies for AD therapy. ApoE is abundantly expressed in the brain and in periphery. In fact, apoE concentration in plasma is about 10 times higher than that in the cerebral spinal fluid. As peripheral apoE, produced mainly by the liver, is separated from brain apoE by the blood-brain barrier (BBB), it is not clear whether and how peripheral apoE affects the function of the central nervous system (CNS) and AD pathogenesis. To address this, we have developed novel mouse models expressing human apoE3 or apoE4 in an inducible, cell type-specific manner. After breeding to albumin-Cre (Alb-Cre) mice which drive apoE expression specifically in the liver, we have generated human apoE3 and apoE4 liver-specific mouse models in the background of murine *Apoe*-KO. Here, we demonstrated that expression of apoE3 in the periphery enhanced synaptic activity and cognition,

whereas expression of apoE4 did the opposite. In addition, peripherally-expressed apoE isoforms differentially affect cerebrovascular integrity and functions, as well as neuroinflammation. Together, our results demonstrate that peripheral expression of apoE isoforms differentially regulates CNS functions. Our findings provide novel mechanistic insights into the pathobiology of apoE4 in AD, and have implications in designing new therapeutic strategies targeting apoE to treat AD.

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**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.02/N11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG045775

BrightFocus Foundation Grant A2014210S

**Title:** Gut microbiome association with APOE genotype in EFAD mice

**Authors: *I. PARIKH**[1,2], J. L. ESTUS[2], M. MALIK[2], L. M. TAI[4,5], M. LADU[4,5], S. J. GREEN[6,5], S. ESTUS[1,2,3]
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**Abstract:** Although the microbiome is emerging as a modulator of the human condition, the role of the microbiome in Alzheimer's disease (AD) is unclear. The *APOE4* genotype is the greatest genetic risk factor for AD and yet has been associated improved gastrointestinal recovery after insult in human and murine studies. These observations lead us to hypothesize that *APOE* genotype impacts the gut microbiome. To assess this hypothesis, we compared 16S ribosomal RNA gene amplicon-based microbiome profiles in EFAD mice, homozygous for *APOE2, APOE3, or APOE4* with both carriers and non-carriers of the 5xFAD mutations at 4 and 6 months of age. Ordination (principal coordinate analyses) of the multivariate data revealed that combining carriers and non-carriers, *APOE* genotype is associated with distinct microbiome profiles, with *APOE3* intermediate between *APOE2* and *APOE4*. Comparisons of the underlying bacterial differences showed that the relative abundance of multiple bacterial families were significantly altered in a step-wise fashion from *APOE4* to *APOE3* to *APOE2*, including bacteria from the family Ruminococcaceae (Clostridia) which were highest with *APOE2*. Bacteria from

this family can be induced by resistant starch diets, and are key for digesting resistant starch to increase short chain fatty acid levels. In summary, we report that the *APOE* genotype is correlated with specific gut microbiome profiles in a murine model, though the mechanism of action is not yet understood. The effect of sex, FAD carrier status and age are important modulators of *APOE* effects and will be investigated, clarifying the potential for translational impact of these data. As well, these data will be strengthened if replicated in other murine model organisms and humans.

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**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.03/N12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** AG04813101

**Title:** The role of APOEs in regulating synaptogenesis

**Authors: *B. ZHOU**, Y.-W. A. HUANG, M. WERNIG, T. C. SUDHOF
Stanford Univ., Stanford, CA

**Abstract:** Apolipoprotein E (ApoE) ApoE4 allele has been identified as the leading risk factor for Alzheimer’s disease (AD). In our previous work, we have shown that ApoE secreted by glia stimulates neuronal APP transcription and Aβ production, with an ApoE4 > ApoE3 > ApoE2 potency rank order, through a non-canonical MAP-kinase pathway (DLK->MKK7->ERK1/2). Here via the human induced neuronal cell co-culturing with MEF system, we found that ApoE also stimulates transcription of synaptic genes and promotes miniature EPSC frequency, with the same potency order of ApoE4>ApoE3>ApoE2. Further mechanism studies indicate that this stimulation is through the same MAP-kinase pathway, but independent from the increased APP transcription.

**Disclosures: B. Zhou:** None. **Y.A. Huang:** None. **M. Wernig:** None. **T.C. Sudhof:** None.

**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.04/O1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH T32 DA007097

NIH R21 AG056025

University of Minnesota College of Pharmacy

University of Minnesota Center on Aging

Academic Health Center of the University of Minnesota

**Title:** Reversing apoE4 lipidation deficiency with a clinically tested HDL mimetic peptide

**Authors: *D. S. CHERNICK**[1], D. A. HOTTMAN[2], A. GRAM[2], L. LI[1,2]
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**Abstract:** Human apolipoprotein E (apoE) exists in three isoforms; the apoE ε4 allele is the primary genetic risk factor for late-onset Alzheimer's disease (AD), while apoE ε2 is protective in AD, and apoE ε3 is neutral. ApoE in the brain is produced and secreted primarily by astrocytes, and binds lipids to form high-density lipoprotein (HDL)-like particles in the interstitial and cerebrospinal fluid. Although the mechanisms by which apoE4 affects the development of AD are not completely understood, compelling evidence indicates that the pathogenic effects of apoE4 are mediated by lipid-related pathways. Compared with the more common apoE3 isoform, apoE4 exhibits deficiency in lipidation and formation of HDL in the brain, whereas apoE2 is lipidated most effectively. ApoE directly interacts with amyloid-β (Aβ), and the level and lipidation state of apoE affects Aβ aggregation and clearance pathways. We have found that a clinically tested 18-aa HDL mimetic peptide, 4F, increases the secretion and lipidation of apoE from primary murine astrocytes. The current study aims to determine whether treatment with 4F can reverse the lipidation deficiency of apoE4. Using immortalized mouse astrocytes expressing the human apoE2, apoE3, and apoE4, respectively, we found that 4F treatment promotes lipidation of all human apoE isoforms. Experiments are underway to determine whether 4F enacts these same effects in primary astrocytes from human apoE isoform (apoE2, apoE3, and apoE4)-targeted replacement (TR) mice. We are also investigating whether treatment with 4F enhances apoE lipidation *in vivo* and mitigates amyloid pathology and memory deficits in mouse models of AD. Our goal is to harness the lipidation power of the HDL-mimetic peptide to reverse apoE4 lipidation deficiency and reduce the risk of AD.

**Disclosures:** **D.S. Chernick:** None. **D.A. Hottman:** None. **A. Gram:** None. **L. Li:** None.

**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.05/O2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Regulation of apolipoprotein E expression and secretion in astrocytes

**Authors: *E. DRESSELHAUS**[1], G. RAMASWAMY[2]
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**Abstract:** Apolipoprotein E (ApoE) is a key lipid transport protein expressed in several cell types and in the brain is predominantly expressed in astrocytes. In the brain it plays critical roles in neuronal repair, synaptogenesis, and clearance of toxic Aβ. Human apoE has three common isoforms, which show a genotype dependent effect on age and risk for late onset and sporadic forms of AD (apoE4>apoE3>apoE2). Despite its association with AD, regulation of apoE in astrocytes is still largely unknown. Currently known mechanism for astrocytic apoE regulation involves nuclear receptors such as liver X receptor (LXR) and retinoid X receptor (RXR). A small molecule phenotypic screen with annotated chemical libraries including Pfizer's chemogenomics library identified three classes of compounds that increased astrocytic apoE secretion: LXR agonists, RXR agonists, and class I HDAC inhibitors. However, the molecular mechanism by which HDAC inhibition leads to apoE secretion is not known. The goal of this project is to delineate the differences in the molecular mechanism by which these three classes of compounds regulate astrocytic apoE. In a human astrocytoma cell line, a time and dose dependent increase in APOE gene expression was observed using both qPCR and RNAseq following cell treatment with the pan-LXR agonist T0901317, the RXR agonist Bexarotene, or the pan-class I HDAC inhibitor MS-275. An increase in gene expression of other genes involved in APOE regulation was also observed, including ABCA1 and LXRα, but not LXRβ. In a co-treatment study, the effects of T0901317 and MS-275 appear to be synergistic for the expression and secretion of APOE but not for other genes tested. Differences in gene expression and cofactor recruitment following treatment with the mentioned compounds can give clues to how APOE expression and secretion is regulated in astrocytes and other cell types.

**Disclosures:** **E. Dresselhaus:** A. Employment/Salary (full or part-time):; Pfizer. **G. Ramaswamy:** A. Employment/Salary (full or part-time):; Pfizer.

**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.06/O3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** ARUK-SPG2013-1

**Title:** Changes in the synaptic proteome in Alzheimer's disease indicate a role for Clusterin and ApoE in synapse degeneration

**Authors: *R. J. JACKSON**[1], A. G. HERRMANN[1], M. LLAVERO[2], C. HENSTRIDGE[1], D. J. LAMONT[3], T. M. WISHART[2], T. L. SPIRES-JONES[1]
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**Abstract:** Of the main pathological features of Alzheimer's disease (AD), synapse loss is the greatest correlate of clinical cognitive decline, and this synapse loss is thought to be central to disease pathogenesis. Although most cases of AD are not directly heritable, genetic risk factors have been identified, the strongest of which is the epsilon 4 isoform of Apolipoprotein E (ApoE4). The ApoE4 allele increases not only the chance of developing AD compared to the more common ApoE3 allele but also increases the rate of cognitive decline seen within the disease. The related Apolipoprotein J or clusterin has also been genetically linked to AD in genome-wide association studies. However, the mechanisms by which AD causes synaptic degeneration and the role that ApoE and Clusterin play in that degeneration remains unclear. Proteomic analysis of synaptoneurosomes isolated from 25 control and 30 Alzheimer's disease patients with known APOE genotypes have indicated that 241 proteins were changed in the AD synapse samples compared to control. Clusterin was found to be significantly upregulated the AD synapse compared with control synapses (fold change 1.63, $p<0.001$). This upregulation was further increased in AD individuals with an ApoE4 genotype compared to those with an ApoE3 genotype (fold change 1.25, $p<0.01$). Fluorescent western blot confirmed this finding in independent cases. Analysis of human post-mortem tissue by array tomography indicates that Clusterin localizes to both the pre and post synaptic densities in a disease and ApoE genotype dependent manner. Array tomography also indicates that clusterin colocalizes with oligomeric Aβ and ApoE protein at the synapse in a disease and ApoE genotype dependent manner, highlighting a potential link between these proteins in synaptic toxicity.
This study investigates the interaction of Clusterin and ApoE at the synapse in post-mortem tissue and shows an ApoE4 genotype dependent increase in the amount of Clusterin at the synapse of AD individuals.

**Disclosures:** **R.J. Jackson:** None. **A.G. Herrmann:** None. **M. Llavero:** None. **C. Henstridge:** None. **D.J. Lamont:** None. **T.M. Wishart:** None. **T.L. Spires-Jones:** None.

**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.07/O4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** VA Grant I01BX002839

NIH Grant R01AG041971

**Title:** Regulation of matrix metallopeptidase 9 by apolipoprotein E

**Authors: *C. RINGLAND**[1], B. SHACKLETON[1], M. EISENBAUM[1], L. ABDULLAH[1], F. CRAWFORD[1], C. BACHMEIER[1,2]
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**Abstract:** Alzheimer's disease (AD) is a neurodegenerative process characterized, in part, by an accumulation of the beta-amyloid (Aβ) protein in the brain and cerebrovasculature. Mounting evidence suggests the excessive accumulation of Aβ in the AD brain is not due to aberrant Aβ production, but the result of impaired Aβ clearance mechanisms. One explanation for the attenuated clearance in AD is dysfunctional Aβ transport at the blood-brain barrier (BBB). The BBB transporter primarily responsible for the brain-to-blood elimination of Aβ is the low density lipoprotein receptor-related protein 1 (LRP1). While LRP1 interacts with an array of ligands, one of the more closely associated is apolipoprotein E (apoE). Previously, we examined the effects of apoE on the proteolytic shedding of LRP1 to its non-functional soluble form. Our results indicate an inverse relationship between LRP1 shedding and Aβ transit across the BBB, one that is apoE isoform-specific. To elucidate the mechanisms driving these observations, we examined the interactions between apoE and a known LRP1 sheddase, matrix metallopeptidase 9 (MMP-9). In a cell-free assay, MMP9 activity was significantly attenuated by apoE in an isoform-specific manner (apoE2>apoE3>apoE4). In apoE4 animals, treatment with an MMP9 inhibitor, SB-3CT, resulted in a significant reduction in brain LRP1 shedding and increased Aβ clearance from the brain to the periphery. Our findings indicate apoE4 is less effective in modulating MMP9 activity and LRP1 shedding than the other apoE isoforms. These studies show that MMP9 modulation can facilitate Aβ removal from the brain, which may provide a novel approach to the treatment of AD, particularly for individuals with an apoE4 genotype.

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**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.08/O5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** ApoE isoforms differentially regulates cleavage and secretion of BDNF

**Authors: *A. SEN**[1], T. J. NELSON[2]
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[2]Blanchette Rockefeller Neurosciences Inst., Morgantown, WV

**Abstract:** Apolipoprotein E4 (ApoE4) is a major genetic risk factor for sporadic or late onset Alzheimer's disease (AD). BDNF is decreased by 3 to 4-fold in the brains of AD patients at autopsy. ApoE4 mice also have reduced brain-derived neurotrophic factor (BDNF) levels. However, there have been no reports relating the different ApoE isoforms or AD to differential regulation of BDNF. Here we report that in the hippocampal regions of AD patients pro-BDNF expression showed a 40% decrease compared to that expression in the hippocampi of age-matched control patients. We further report that ApoE isoforms differentially regulate maturation and secretion of BDNF from primary human astrocytes. After 24 hours, ApoE3 treated astrocytes secreted 1.75- fold higher pro-BDNF than ApoE2-treated astrocytes, and ApoE2-treated astrocytes secreted 3-fold more mature-BDNF (m-BDNF) than ApoE3-treated astrocytes. In contrast, ApoE4-treated cells secreted negligible amounts of m-BDNF or pro-BDNF. ApoE2 increased the level of intracellular pre-pro BDNF by 19.04 ± 6.68 %, while ApoE4 reduced the pre-pro BDNF by 21.61 ± 5.9 % compared to untreated cells. Similar results were also seen in ApoE2, ApoE3 or ApoE4 treated cells at 4 hr. Together, these results indicate that an ApoE2 or ApoE3 mediated positive regulation of BDNF may be protective while ApoE4 related defects in BDNF processing could lead to AD pathophysiology. These interactions of the ApoE isoforms with BDNF may help explain the increased risk of AD associated with the ApoE4 isoform.

**Disclosures: A. Sen:** None. **T.J. Nelson:** None.

**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.09/O6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH 5T32GM008151-32 (MX)

NIH R01AG047644 (DMH)

a research grant from Denali Therapeutics (DMH)

**Title:** Anti-apoE antibodies reduced amyloid pathology by active recruitment of microglia in APPPS1-21/apoE4 mice

**Authors: *M. XIONG**[1], F. LIAO[1], N. BIEN-LY[2], A. P. SILVERMAN[2], R. J. WATTS[2], J. REMOLINA SERRANO[1], M. FINN[1], P. SULLIVAN[3], H. JIANG[1], J. D. ULRICH[1], D. M. HOLTZMAN[1]
[1]Washington Univ. Sch. of Med., Saint Louis, MO; [2]Denali Therapeut., South San Francisco, CA; [3]Duke Univ., Durham, NC

**Abstract:** Apolipoprotein E (*APOE*) gene is the strongest genetic risk factor for sporadic, late-onset Alzheimer's disease (AD). The ε4 allele of human apoE (apoE4) slows amyloid-β (Aβ) clearance (Castellano et al., 2011) and induces Aβ fibril aggregation (Ma et al., 1994). Previous work has shown that a monoclonal antibody against murine apoE decreased plaque load when administered intraperitoneally to a mouse model of amyloidosis when given either before (Kim et al., 2012) or after (Liao et al, 2014) the onset of plaque deposition. Our current study aimed to further investigate the therapeutic effects of apoE antibodies. We hypothesized that certain anti-apoE antibodies that specifically bind apoE would reduce amyloid pathology via a microglial-mediated mechanism. We initially characterized different anti-apoE antibodies and selected an antibody for further *in vivo* experiments based on its overall binding properties to apoE. In a 6-week treatment regimen, antibody administration to 2-month APPPS1-21/apoE4 mice (n=10-13/group) at 50 mg/kg/week reduced Aβ plaque load ($p<0.05$, one-way ANOVA, Tukey post-hoc test). Following acute administration of anti-apoE antibodies (50 mg/kg, 4 injections every 3 days), we detected an increase in plaque-associated staining with the microglial marker CD45 in the antibody-treated mice ($p<0.05$). These results suggest that binding of the anti-apoE antibody may trigger the active recruitment of microglia to plaques. Anti-apoE antibodies may serve as a viable therapeutic strategy for targeting Aβ plaques in AD.

**Disclosures:** **M. Xiong:** None. **F. Liao:** A. Employment/Salary (full or part-time):; Abbvie. **N. Bien-Ly:** A. Employment/Salary (full or part-time):; Denali Therapeutics. **A.P. Silverman:** A. Employment/Salary (full or part-time):; Denali Therapeutics. **R.J. Watts:** A. Employment/Salary (full or part-time):; Denali Therapeutics. **J. Remolina Serrano:** None. **M. Finn:** None. **P. Sullivan:** None. **H. Jiang:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Intellectual property related to Denali. **J.D. Ulrich:** None. **D.M. Holtzman:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research grant from Denali. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind

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**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.10/O7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Differential effects of human and mouse apolipoprotein E on the metabolism and aggregation of amyloid-β peptides

**Authors: *A. KOKAWA**, Y. OHNO, T. HASHIMOTO, T. IWATSUBO
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**Abstract:** Alzheimer's disease (AD) is the most common neurodegenerative disease causing dementia, and massive deposition of amyloid-β peptide (Aβ) as senile plaques in the brain is the pathological hallmark of AD. Apolipoprotein E (apoE) plays an important role in the lipid transport in the brain. There are three common alleles of the human *APOE* gene (*ε2*, *ε3*, and *ε4*), which give rise to differences at one or two amino acid sequence positions of the protein products. Among *APOE* genes, *APOE ε4* allele is the major genetic risk factor for AD, whereas it is still unknown how apoE impacts the Aβ metabolism in the brain. Mouse apoE protein shares ~70% homology with human apoE. To compare the effects of human apoE on Aβ metabolism in the brain with those of mouse apoE, we examined APP transgenic mice (APPswe/PS1deltaE9 line) and those crossed with human apoE3 knock-in mice (APP mice and APP/apoE3 KI mice, respectively). First, we immunostained cortices of 9-month-old APP or APP/apoE3 KI mice with an anti-Aβ or anti-apoE antibodies and found that the Aβ burden in APP/apoE3 KI mice was significantly lower than that in APP mice. We observed co-deposition of human apoE3 or mouse apoE with Aβ in the plaques. We next performed *in vivo* microdialysis in 3-month-old APP or APP/apoE3 KI mice to assess the Aβ metabolism in the hippocampal interstitial fluid (ISF). After measuring the baseline concentration of ISF Aβ, we perfused a γ-secretase inhibitor into the hippocampus and sequentially collected the ISF samples to analyze the half-life of Aβ in the brain. The concentration and the half-life period of ISF Aβ in the hippocampus of APP mice and APP/apoE3 KI mice were at similar levels. In addition, the levels of lipidated apoE in the Tris-soluble fraction of the brain of APP/apoE3 KI mice was comparable with that in APP mice as determined by gel filtration analysis. Finally, we conducted *in vitro* ThioflavinT (ThT) binding assays to examine the effects of human or mouse apoE on the fibrillization of Aβ. Synthetic Aβ42 was incubated alone, or in the presence of recombinant human apoE3 or mouse apoE, and then the formation of Aβ fibrils were assayed by ThT. In comparison with the incubation of Aβ alone, coincubation with human apoE3 delayed the start of Aβ fibril formation. Notably, mouse

apoE was less effective in inhibiting the Aβ fibril formation than human apoE3. In conclusion, our data suggest that human apoE3 suppresses Aβ fibril formation more strongly than mouse apoE. This may explain the lesser Aβ deposition in APP/apoE3 KI mice compared with APP mice.

**Disclosures:** **A. Kokawa:** None. **Y. Ohno:** None. **T. Hashimoto:** None. **T. Iwatsubo:** None.

**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.11/O8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH grant R01AG047644

JPB Foundation

**Title:** ApoE facilitates the microglial response to amyloid pathology

**Authors:** ***J. D. ULRICH**[1], T. K. ULLAND[2], T. E. MAHAN[2], P. NILSSON[3], W. SONG[2], H. JIANG[2], F. STEWART[2], E. ANDERSON[2], Y. WANG[2], M. COLONNA[2], D. HOLTZMAN[2]
[1]Neurol. Dept., Washington Univ. of St Louis, Saint Louis, MO; [2]Washington Univ., St. Louis, MO; [3]Linkoping Univ., Linkoping, Sweden

**Abstract:** One of the hallmarks of Alzheimer's disease is the presence of extracellular diffuse and fibrillar amyloid plaques predominantly consisting of the amyloid-β (Aβ) peptide. Activated microglia cluster around Aβ plaques, although the physiological mechanism facilitating microglial clustering is still poorly understood. The formation of Aβ plaques within the brain parenchyma is influenced both by the concentration of monomeric forms of Aβ in the interstitial fluid and by other proteins in the brain, perhaps most notably apolipoprotein E (apoE). ApoE has previously been shown to influence the rate of Aβ clearance from the brain interstitial fluid in an isoform-dependent manner, and to influence the kinetics of amyloid formation in vitro. Both of these characteristics likely contribute to apoE-dependent effects on Aβ plaque formation in vivo. In addition to influencing Aβ metabolism, increasing evidence suggests that apoE expression may influence the microglial response in the context of neurodegenerative disease. ApoE is strongly upregulated by microglia in the context of Aβ pathology and ApoE has been shown to bind to the microglial receptor, TREM2, which has been implicated in regulating microglial response to amyloid plaques. Although chronic microglial activation is hypothesized to result in neurotoxic inflammatory signaling, recent studies found that plaque-associated microgliosis was negatively correlated with the degree of neuritic dystrophy around plaques, suggesting a potential protective role for microglia, at least in responding to amyloid plaques.

The effect of apoE expression in amyloid mouse models on the glial response to amyloid pathology is not currently understood. In this study, we characterize the impact that apoE has on amyloid pathology and the innate immune response in the APPPS1ΔE9 and APPPS1-21 amyloid mouse models. We find that Apoe KO mice exhibited reduced fibrillar plaque deposition and altered regional distribution of plaque pathology within the hippocampus, consistent with previous studies. However, the fibrillar plaques that were present in Apoe KO mice exhibited a striking reduction in plaque compaction and hyperspectral fluorescent imaging using luminescent conjugated oligothiophenes identified distinct Aβ morphotypes in Apoe KO mice. We also observed a significant reduction in plaque-associated microgliosis and activated microglial gene expression in Apoe KO mice, along with significant increases in dystrophic neurites. Our results suggest that apart from influencing Aβ plaque formation, apoE facilitates plaque-associated microgliosis and limits plaque-associated neuronal toxicity.

**Disclosures: J.D. Ulrich:** None. **T.K. Ulland:** None. **T.E. Mahan:** None. **P. Nilsson:** None. **W. Song:** None. **H. Jiang:** None. **F. Stewart:** None. **E. Anderson:** None. **Y. Wang:** A. Employment/Salary (full or part-time):; Eli Lilly. **M. Colonna:** None. **D. Holtzman:** None.

**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.12/O9

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** JSPS KAKENHI 15K06781

**Title:** Apolipoprotein e containing lipoproteins prevent optic nerve degeneration with a reduction of alpha 2 macroglobulin secretion from retinal glia

**Authors: *H. HAYASHI**, M. MORI, M. HARASHIMA, T. HASHIZUME, M. FURIYA, H. MORI, B. YUAN, N. TAKAGI
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**Abstract:** Lipoproteins secreted from glial cells have important roles in lipid metabolism and transport of the central nervous system (CNS). Apolipoprotein (apo) E is a major apo in the CNS. It has been known that apo E-containing glial lipoproteins not only supply lipids to neurons but also cholesterol in apo E-containing glial lipoproteins promotes synaptogenesis in CNS neurons. We have reported that apo E-containing glial lipoproteins stimulate axon growth of retinal ganglion cells and protect retinal ganglion cells from apoptosis induced by trophic factor-withdrawal via low density lipoprotein receptor-related protein 1 (LRP1). It has also been shown that alpha2-macroglobulin (a2M), which is known as an LRP1 ligand, is increased in aqueous humor of glaucoma patients. Here, we demonstrate that apo E-containing lipoproteins

prevent retinal damage induced by intravitreal injection of *N*-methyl-D-aspartate in rats and decrease a secretion of a2M from primary cultured retinal glia. The protective effect of apo E-containing lipoproteins against excitotoxicity in primary cultured retinal ganglion cells was interfered with a2M, but exogenous treatment of the lipoproteins overcame the interference. Administration of apo E-containing lipoproteins into culture medium decreased mRNA and protein levels of a2M in a receptor-mediated manner in primary cultured retinal glia. These findings suggest a potential therapeutic strategy of apo E-containing lipoproteins or LRP1 agonists by reducing a2M levels in the retinal glia as treatments for neurodegenerative disorders of the retina, such as glaucoma.

**Disclosures: H. Hayashi:** None. **M. Mori:** None. **M. Harashima:** None. **T. Hashizume:** None. **M. Furiya:** None. **H. Mori:** None. **B. Yuan:** None. **N. Takagi:** None.

**Poster**

**476. The Role of ApoE in Mechanisms of Neurotoxicity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 476.13/O10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG04813101

**Title:** ApoE2, E3 and E4 differentially activate MAP-kinase signaling to promote synaptogenesis, APP transcription and Aβ secretion paralleling their role in Alzheimer’s Disease

**Authors: *Y.-W. A. HUANG**[1], B. ZHOU[1], M. WERNIG[2], T. C. SÜDHOF[1]
[1]Mol. and Cell. Physiol., [2]Pathology and Inst. for Stem Cell Biol. and Regenerative Med., Stanford Univ. Sch. of Med., Stanford, CA

**Abstract:** The apolipoprotein ApoE4 allele is the most important genetic risk factor for Alzheimer’s disease (AD), whereas the ApoE2 allele is protective. How ApoE influences AD pathogenesis, however, remains unclear. Using homogeneous populations of pure human neurons derived from ES cells, we show that ApoE binding to neuronal ApoE-receptors activates MAP-kinase signaling via dual leucine-zipper kinase independent of cholesterol, which in turn promotes synaptogenesis by stimulating transcription of synaptic genes and of APP. Strikingly, ApoE4 activated MAP-kinase signaling significantly more and ApoE2 significantly less potently than ApoE3. CRISPRi-mapping of the APP promoter showed that ApoE activated APP transcription via an AP-1-binding site. Stimulation of APP synthesis by ApoE significantly increased Aβ production, again with a rank potency order of ApoE4>ApoE3>ApoE2. Our data suggest that ApoE4 may predispose to AD by inducing a small chronic increase in neuronal MAP-kinase signaling, APP production, and Aβ synthesis, and that interference with ApoE-stimulated APP transcription may delay AD pathogenesis.

**Disclosures:** **Y.A. Huang:** None. **B. Zhou:** None. **M. Wernig:** None. **T.C. Südhof:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.01/P1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Local funds from Torino University

**Title:** Abeta42 oligomers impair NMDA receptors function: A model for studying the early synaptic alterations following Alzheimer’s disease onset

**Authors: *A. MARCANTONI**, M. CERULLO, P. BUXEDA, V. CARABELLI, E. CARBONE
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**Abstract:** We have recently defined the mechanisms of calcium dyshomeostasis induced by Abeta42 showing that, while Abeta42 stimulates $Ca^{2+}$ release from ryanodine receptors (RyRs), it inhibits $Ca^{2+}$ entry through voltage gated $Ca^{2+}$ channels (VGCCs) and NMDA receptors (NMDARs)[1]. It is known that NMDARs are important for controlling neuronal plasticity, learning and memory processes and that these brain functions are altered during aging [2] as well as in AD [3]. These previous observations have suggested a more detailed study of the effects of Abeta42 on NMDARs activated currents. Patch clamp experiments revealed that the average inward current carried by NMDARs previously activated by the selective agonist NMDA (50 µM) was significantly decreased by Abeta42 oligomers (from 352.3±52.7 pA (n=31) to 117.3±15.4 (n=23)). By comparing the dose response curves obtained by increasing the NMDA concentration from 2 to 300 µM and fitted by the Hill equation, we did not observe any change induced by Abeta42 administration ($K_d$ and n values were 17.3±3.3 and 1.4±0.4 in control vs 16.5±3.3 1.5±0.4 in the presence ofAbeta42). We concluded that Abeta42 does not affect the ligand-receptor binding process. We next estimated the unitary current and the number of NMDARs from variance analysis [4] observing that Abeta42 decreases the total number of NMDARs without altering their conductance. By performing calcium imaging experiments we quantified the total amount of intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_i$) before and after exposure of neurons to Abeta42. We observed that NMDA administration induced an 8-fold increase of $[Ca^{2+}]_i$ and that, in good agreement with that observed in patch clamp experiments, Abeta42 almost halved this effect. Further experiments revealed that $Ca^{2+}$ entry through NMDARs is accompanied by $Ca^{2+}$ release from the stores. When we focused on the role of RyRs we observed that the overall amount of $[Ca^{2+}]_i$ increase measured after NMDA administration was half-dependent by RyRs and that Abeta42, despite increasing the amount of $Ca^{2+}$ released by RyRs[1] and decreasing the number of NMDARs, did not change this proportion. We concluded that Abeta42 impairs NMDARs function and that this may occur during the early stages of AD onset.

The development of selective modulators of these receptors may be useful for developing effective therapies that could enhance the quality of life of AD patients.

**References**

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**Disclosures: A. Marcantoni:** None. **M. Cerullo:** None. **P. Buxeda:** None. **V. Carabelli:** None. **E. Carbone:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.02/P2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** MINECO-FEDER (BFU2014-56164-P)

Fundación Tatiana Perez de Guzmán el Bueno

ISR held a predoctoral fellowship from UCLM.

**Title:** G-protein gated inwardly-rectifying potassium (Kir3/GirK) channel activation rescues synaptic, network, and cognitive hippocampal functions in an *In vivo* murine model of early Alzheimer’s disease

**Authors: *I. SÁNCHEZ-RODRÍGUEZ**[1], S. TEMPRANO-CARAZO[1], A. NÁJERA[1], S. DJEBARI[1], J. YAJEYA[2], A. GRUART[3], J. DELGADO-GARCIA[3], L. JIMÉNEZ-DÍAZ[1], J. D. NAVARRO-LOPEZ[1]
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**Abstract:** The hippocampus plays a critical role in learning and memory processes. Its correct performance relies on excitatory/inhibitory synaptic transmission balance. Neuronal hyperexcitabillity in the hippocampus is one of the most distinctive hallmarks in early stages of Alzheimer’s disease (AD). This imbalance may emerge from inhibitory neurotransmission impairments, rather than an increase in excitatory activity, and has been related to the network dysfunction observed at those early stages of the disease. G-protein gated inwardly-rectifying potassium (GirK) channels induce neurons to hyperpolarize, thus acting as restrictors of the neuronal excitation excess. As we have previously shown *in vitro*, amyloid-$\beta$ (A$\beta$) peptides, which have a causal role as the main neurotoxic in AD pathogenesis, disrupt GirK channels at

the molecular and synaptic levels. In this work we have examined the role of GirK channels in an *in vivo* murine model of AD. We aimed to analyse the relationship between GirK channels and the hippocampal dysfunction developed in amyloid-$\beta$ pathology. In order to reach that objective, we performed acute intracerebroventricular injections of A$\beta_{1\text{-}42}$ peptide in fully alert behaving mice to create a non-transgenic model of AD. The effect of said injections was studied: 1) at the synaptic level, by using I/O and PPF protocols in CA3-CA1 synapse, 2) at the circuit and network levels, by studying oscillatory properties of CA1 region and LTP induction in CA3-CA1 synapse and 3) at the behavioral level, on learning and memory capabilities during an object recognition test, which depends on CA3-CA1 synapse performance. Our data suggest that GirK channels are necessary for normal hippocampal activity at synaptic, neural network and behavioral levels. An imbalance on GirK activity results on excitability, LTP and learning abnormalities. Interestingly, we found that an increase in GirK activity on A$\beta$-injected mice restores hippocampal excitability levels increased by the amyloid peptide in the CA3-CA1 pathway, and therefore counteracts hippocampal synaptic plasticity, network oscillatory activity, and memory deficits induced by A$\beta$. Taken together, our results support the assertion that corrections focused on the prevention of network hyperexcitability, for example by increasing GirK channels activity, would provide new therapeutic approaches for AD pathogenesis. GirK channels modulation emerges as a promising tool to improve AD related memory deterioration and underlying network signaling and synaptic neurotransmission aberrations.

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**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.03/P3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Fyssen Foundation

France Alzheimer

LECMA

IUF

**Title:** Early disruption of parvalbumin expression and perineuronal nets in the hippocampus of the Tg2576 mouse model of Alzheimer's disease

**Authors: V. CATTAUD**, C. BEZZINA, C. REY, C. LEJARDS, L. DAHAN, *L. VERRET
CRCA CNRS Toulouse, Toulouse, France

**Abstract:** Alzheimer's disease (AD) results in deterioration of cognitive functions linked to abnormal patterns of brain activity. Our recent findings indicate that transgenic mouse lines resembling key features of AD have impaired parvalbumin(PV)-expressing inhibitory fast-spiking interneuron function, which can be linked to network hypersynchrony, aberrant oscillatory activity, and memory deficits. In the mature brain, PV cells are often associated with a specific form of extracellular matrix, the perineuronal net (PNN). Indeed, PNN are appearing around PV cells at critical period of cortical maturation and are ensuring the stabilization of existing synapses. Moreover, loss of PNN in the hippocampus is often associated with aberrant hippocampal plasticity and function.
Thus, we wondered whether modifications of PNN around PV cells could participate to aberrant brain network activities observed in AD mice. To address this question, we performed stainings for PV and PNN in the hippocampus of 3, 6 and 13-month-old Tg2576 and non-transgenic (NTg) mice. Our data show a deficit of PV+ and/or PNN+ cells as young as 3-month-old in the CA1, CA2, and CA3 of Tg2576 mice, and a disruption of PNN before PV+ cells decrease. This is suggesting that PV+ cell plasticity is an early event in the course of the pathology of this AD mouse model.
We also tested whether the long-lasting beneficial effect of transient enriched environment (EE) can be sustained by a change in PV cell plasticity. To do so, Tg2576 and NTg mice were transiently exposed to EE between 3 and 5.5 months of age that has proven long-lasting effect on memory functions in this mouse line. We observed a rescue of PV cell number in the hippocampus of Tg2576 mice following transient EE, suggesting that the beneficial behavioral effect of environmental stimulations might be sustained by improving the basal activity of PV cells rather than by restoring their PNNs.

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**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.04/P4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** SAF2012-38316

**Title:** Cell cycle re-entry followed by hyperploidy triggers synaptic dysfunction in differentiated cortical neurons: An Alzheimer's disease mechanism?

**Authors: *E. BARRIO-ALONSO**[1,2], A. HERNÁNDEZ-VIVANCO[3], C. C. WALTON[2], G. PEREA[3], J. M. FRADE[2]
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**Abstract:** Cell cycle re-entry, followed by hyperploidization of differentiated neurons, and synaptic failure are two known events taking place at the earliest stages of Alzheimer's disease (AD), but their functional connection remains unexplored. To address this question, we used differentiated cortical neurons that were forced to reactivate the cell cycle by SV40 large T antigen (TAg) expression, evidenced by an 80% of BrdU incorporation in NeuN+ neurons two days after transfection together with an increase of DNA content. We show that cell cycle re-entry specifically leads to reduced spontaneous electrical activity and diminished spike generation in cortical neurons. This is followed by delayed non-apoptotic cell death independent on oxidative stress. We also show that membrane depolarization by KCl partially rescues TAg-dependent neuronal death even though electrical capacity of TAg-transfected neurons remains reduced, thus suggesting that the survival of AD-associated hyperploid neurons may depend on their insertion in active neuronal circuits. Our results indicate that cell cycle reentry in neurons may actively participate in the AD etiology.

**Disclosures: E. Barrio-alonso:** None. **A. Hernández-vivanco:** None. **C.C. Walton:** None. **G. Perea:** None. **J.M. Frade:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.05/P5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** KAKENHI 17H05062

**Title:** Analysis of synaptic insulin signaling in the hippocampus and prefrontal cortex in diabetes-associated cognitive impairment

**Authors: *H. TADA**[1,2], A. TOKUNAGA[2], D. TANOKASHIRA[2], M. KASHIWADA[2], T. SAJI[2], M. IMAI[2], A. TAGUCHI[2]
[1]Dept. of integrative aging neuroscience, [2]Natl. Ctr. for Geriatrics and Gerontology, Obu, Japan

**Abstract:** The synaptic activity in the hippocampus and PFC is important for cognitive functions. Synaptic dysfunction is a distinctive neural alternation in the early stages of dementia and related to the progression of clinical symptoms. Epidemiological studies have shown that

Diabetes Mellitus (DM) is a risk factor for dementia, and the progression of cognitive impairment is accelerated by DM. Alteration in neural insulin signaling may be associated with pathogenesis of DM-related cognitive impairment. However, the mechanism of the interaction between neural insulin signaling and synaptic dysfunction is largely unknown. Our recent work showed that activated hippocampal insulin signaling correlates with cognitive impairment in the physiological type 2 diabetes model (DIO: Diet Induced Obesity) mice. Furthermore, we found that insulin signaling components are localized not only in cytoplasm but also in the postsynaptic density (PSD), and synaptic insulin signaling is upregulated in both the hippocampus and prefrontal cortex (PFC) of DIO mice. Finally, we confirmed that DIO mice exhibited impaired working memory via hippocampus and PFC network in the reversal Water T-maze test. Thus, these results suggested that DM-induced upregulation of synaptic insulin signaling may facilitate hippocampus and PFC dependent cognitive impairment.

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**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.06/P6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** This work was supported by funds from Maestro grant to JK from a National Science Centre (2011/02/A/NZ3/00144)

**Title:** Synaptic plasticity and animal behavior can be modulated by playing with the STIMs and ORAIs expression in neurons - The key players in the store operated calcium entry

**Authors: *L. MAJEWSKI**[1], *L. MAJEWSKI[1], F. MACIAG[1], P. M. BOGUSZEWSKI[2], J. KUZNICKI[1]
[1]Lab. of Neurodegeneration, Intern. Inst. of Mol. and Cell Biol., Warszawa, Poland; [2]Lab. of Animal Models, Neurobio. Centre, Nencki Inst. of Exptl. Biol. of the Polish Acad. of Sci., Warsaw, Poland

**Abstract:** Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder. At least two types of AD can be distinguished: sporadic AD (SAD) of unknown etiology, which accounts for most cases, and genetically encoded familial AD (FAD), which affects up to 5% of all of the patients. The most widely accepted risk factor for developing Alzheimer’s disease is age. It has been shown that during brain ageing, subtle but sustained changes in calcium homeostasis occur.
Store-operated calcium entry (SOCE) is the major $Ca^{2+}$ influx pathway in non-excitable cells.

However, recent body of evidence indicates that SOCE plays an important role in brain neurons. SOCE is a process by which the depletion of $Ca^{2+}$ from the endoplasmic reticulum (ER) causes an influx of $Ca^{2+}$ from the extracellular space to replenish the intracellular stores. STIM1 and STIM2 are calcium ER sensors mediating the process of SOCE by interacting with the ion channels in the cell membrane - ORAIs. Our group showed that the cytoplasmic resting $Ca^{2+}$ level in primary rat cortical neurons can be modulated by overexpression of STIM proteins. We also detected an enhanced magnitude of $Ca^{2+}$ influx during SOCE in human lymphocytes from SAD patients.
The objective of our research is to understand how elevated basal $Ca^{2+}$ level in neurons contributes to neurodegeneration. We have already obtained transgenic mice with elevated gene expression of STIM1, STIM2 or ORAI1 specifically in brain neurons. In one of our recent papers we described the line overexpressing STIM1 [FVB\NJ-Tg(STIM1)Ibd], which exhibited impairments in long term depression and behavior. Using neuronal calcium fluorescent imaging combined with electrophysiology and behavioral tests we now analyze phenotype of the mice lines overexpressing STIM2 or ORAI1. We have found that FVB\NJ-Tg(STIM2)Ibd lines exhibit anxiety - related changes in behavior but no alternations in synaptic plasticity in CA3-CA1 hippocampal projection, wheareas FVB\NJ-Tg(ORAI1)Ibd mice demonstrate changes in the distribution of miniature excitatory postsynaptic currents (mEPSCs) amplitudes. The obtained lines can be suitable models for further analysis of the hypothesis that brain dysfunction during ageing is induced by changes in $Ca^{2+}$ homeostasis.

**Disclosures:** **L. Majewski:** A. Employment/Salary (full or part-time):; International Institute of Molecular and Cell Biology in Warsaw. **F. Maciag:** A. Employment/Salary (full or part-time):; International Institute of Molecular and Cell Biology in Warsaw. **P.M. Boguszewski:** None. **J. Kuznicki:** A. Employment/Salary (full or part-time):; International Institute of Molecular and Cell Biology in Warsaw.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.07/P7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant RO1NS084965

**Title:** Age-dependent changes in the synaptic regulator arc (activity-dependent cytoskeleton-associated protein) in the hippocampal formation of mice

**Authors: *A. KHAN**[1,2], K.-C. LEE[1], H.-Y. WANG[1,2]
[1]Dept Physiol, Pharmacol & Neurosci, CUNY Sch. of Med., New York, NY; [2]Biol., The Grad. Center, City Univ. of New York, New York, NY

**Abstract:** Introduction: Activity-dependent cytoskeleton-associated protein (Arc) is a postsynaptic, neuron specific protein. Arc is a prominent regulator of synaptic plasticity and homeostasis (Korb and Finkbeiner, 2011). Specifically, Arc is involved in AMPA receptor endocytosis and late phase LTP consolidation at the dendrite. NMDA receptor activation drives up Arc expression to promote remodeling of the dendritic spine via its direct and indirect interactions with dendritic spine proteins such as cofilin and the actin cytoskeleton. Given that synaptic activity is reduced in an age-dependent manner and markedly deteriorated in Alzheimer's disease (AD), we propose the hypothesis that basal and activity-driven Arc expression are altered during normal aging and in AD pathogenic progression. To this end, we investigated Arc expression under non-stimulated (basal) and NMDA/Glycine stimulated conditions in hippocampal formation (HF) from 3-, 6-, 10- and 15-month old wild-type (WT) and 3x transgenic (Tg) AD mice. Methods: A well-established, ex-vivo stimulation method (Wang, H.-Y., J. Neurosci, 9: 9773-9784, 2012) was used to assess Arc levels in response to Kreb's Ringer (control) and NMDA/glycine. Arc in the solubilized HF slices was isolated by immunoprecipitation with anti-Arc antibodies and determined using western blotting. Simultaneously, β-actin purified by anti-actin antibody was used as the immunoprecipitation/loading control. Results: Basal Arc expression is elevated in 3xTg AD mice at 6-month of age. NMDA/glycine-stimulated Arc expression is reduced in 3X Tg AD mice of all ages and in WT > 10 months of age. Conclusions: Our data suggest that activity-driven Arc expression is a sensitive indicator for assessing the magnitude of synaptic dysfunction during both the aging process and, more significantly, AD pathogenesis.

**Disclosures: A. Khan:** None. **K. Lee:** None. **H. Wang:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.08/P8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA Grant AG043552-05

Alzheimer's Association Grant 2015-NIRG-339422

**Title:** Amyloid-β induces dendritic degeneration by altering Rho kinase (ROCK) signaling in Alzheimer's disease

**Authors: *B. W. HENDERSON**, J. H. HERSKOWITZ
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**Abstract:** Current estimates project that there are approximately 5.4 million Americans affected by Alzheimer's disease (AD). Cognitive decline is a clinical hallmark of AD, while accumulation of amyloid-β (Aβ) is a pathological hallmark. Aβ accumulates prior to synapse loss in AD, and synapse loss correlates more strongly with cognitive decline than classical pathologic hallmarks. Yet, there are few therapeutic strategies that target synapse loss as a mechanism to delay or prevent cognitive decline in AD. RhoA, a Rho GTPase family member, and its primary downstream effectors, the Rho-associated coiled-coil containing protein kinases (ROCK) 1 and ROCK2, are potent regulators of actin dynamics, influencing neuronal morphology and synaptic plasticity. Our previous work demonstrated that ROCK1 and ROCK2 protein levels are increased in mild cognitive impairment due to AD (MCI) and AD cases, and that Aβ activates the RhoA/ROCK pathway. We show that Aβ induces dendritic spine degeneration in primary hippocampal neurons, but treatment with Fasudil, a clinically available pan-ROCK inhibitor, prevents Aβ-induced spine loss. Moreover, we define how pharmacologic or genetic manipulation of ROCKs interacts with Aβ's negative impact on dendritic spine physiology in hippocampal neurons. Using three-dimensional modeling of dendritic structure, we define isoform-specific effects of ROCKs on dendritic spine density and morphology. Our findings highlight key role for ROCKs in dendritic degeneration and continue to support a notion for ROCK inhibition as a viable treatment for cognitive decline in AD progression.

**Disclosures: B.W. Henderson:** None. **J.H. Herskowitz:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.09/P9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** In diabetic rats, insulin within the hippocampus increased

**Authors: *A. S. SHINGO**[1], S. KITO[2], T. MURASE[1]
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**Abstract:** Hitherto, we have clarified the mechanism of the cognitive decline in intracerebroventricularly streptozotocin-injected rats (STZ-3V rats). These rats showed impaired spatial memories and decreased immunoreactivities for hippocampal pCREB, AKT, IDE and SST together with increased immunoreactivity for Ab protein. They are considered a model of Alzheimer's disease. Furthermore, we demonstrated the immediate recovery from cognitive impairments in STZ-3V rats following one shot intracerebral injection of insulin detemir. Based on these results, we proceeded to study how cognitive dysfunction in type 2 diabetes is related to intracerebral insulin signalling and measured the amount of insulin within the hippocampus. The

new-born Wistar strain rats were prepared for type 2 diabetes mellitus (DM2T) by intraperitoneal injection of streptozotocin 2-3 days after birth. After the 4-week-old rats were imposed for Morris water maze test, immnohistochemical staining for insulin-signalling-related substances along with amyloid beta (Ab) protein were done. The insulin within the hippocampus was quantitatively assayed by ELISA.The DM2T rats showed impaired spatial memories and decreased immunoreactivities for hippocampal pCREB, AKT, IDE and SST along with increased immunoreactivity for Ab protein exactly as observed in STZ-3V rats. Insulin within the hippocampus was increased compared to the hippocampus in control rats contrary to our initial expectation of brain insulin deficiency in diabetes. It was concluded that there was the insulin resistance in DM2T hippocampus which leads to cognitive impairments accompanied by Alzheimer's disease-like cerebral changes.

**Disclosures: A.S. Shingo:** None. **S. Kito:** None. **T. Murase:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.10/P10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA Grant AG043552-03

Alzheimer's Association Grant 2015-NIRG-339422

**Title:** Dendritic spine structural remodeling provides cognitive resilience against Alzheimer's disease pathology

**Authors: *B. D. BOROS**[1], E. G. GENTRY[1], E. L. BIRCHALL[1], M. GEARING[2], J. H. HERSKOWITZ[1]
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**Abstract:** Approximately 30-50% of individuals who come to autopsy without dementia have high levels of Alzheimer's disease (AD) pathology. These cases are proposed to represent individuals who are resilient to dementia, but how cognitively normal older individuals with AD pathophysiology withstand the development of dementia has remained one of the most pivotal, unanswered questions in the field. Here we used innovative, highly optimized three-dimensional modeling of dendritic spines to analyze synapse populations from controls, cognitively normal individuals with high AD pathology, and AD dementia cases. Our analysis shows that dendritic spines undergo unique structural remodeling exclusively in patients with high AD pathology but no cognitive impairment. Samples included postmortem human prefrontal cortex tissue from age-matched pathology-free controls, controls with high levels of AD pathology (CAD), and

late-onset AD cases. Methods included Golgi-Cox technique, brightfield imaging, three-dimensional digital reconstruction and morphological analysis of dendritic spines. We compared the density of dendritic spines within layers II and III pyramidal neuron dendrites in Brodmann Area 46 dorsolateral prefrontal cortex, a key area of working memory, using the Golgi-Cox technique in control, CAD, and AD cases. We developed a method to digitally trace impregnated dendrites from brightfield microscopy images, enabling accurate three-dimensional reconstruction of dendritic structure. Analysis of spine morphology revealed unique structural remodeling of synapses exclusively in CAD cases compared to controls or AD. These results bridge gaps to link non-human primate models of age-related memory loss with human dementia. Our findings support the hypothesis that spine plasticity is a mechanism of cognitive resilience that protects older individuals with AD pathophysiology from developing dementia and highlight structural plasticity as a substrate for therapeutic intervention to delay dementia onset during the preclinical phase of AD.

**Disclosures: B.D. Boros:** None. **E.G. Gentry:** None. **E.L. Birchall:** None. **M. Gearing:** None. **J.H. Herskowitz:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.11/Q1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Evidence that mitochondrial sirt3 protects neuronal networks against amyloid β-peptide toxicity by constraining excitability

**Authors: *N. R. GHENA**[1], Y. LIU[1], A. CHENG[2], M. P. MATTSON[2]
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**Abstract:** Alzheimer’s disease (AD) is neurodegenerative disorder characterized by progressive cognitive impairment and aberrant behavior. Although amyloid β-peptide (Aβ) accumulation is a diagnostic criterion for AD, it has become evident that neuronal circuits can resist and/or compensate for Aβ cytotoxicity as demonstrated by cognitively intact individuals with extensive Aβ deposits, and transgenic mice that accumulate massive amounts of Aβ but no neuronal death. Mitochondrial impairment is implicated as an early event in AD pathogenesis. We recently reported that the mitochondrial protein deacetylase SIRT3 protects neurons against excitotoxic and metabolic stress by mechanisms involving enhanced removal of mitochondrial superoxide and inhibition of apoptosis (*Cell Metab.* 2016; 23:128-142). Here we report that AD patients exhibit a marked reduction in SIRT3 levels in vulnerable, but not in minimally vulnerable, brain regions suggesting a potential role for diminished SIRT3 in AD pathogenesis. Because it has

been known since the early 1990s that Aβ renders neurons vulnerable to excitotoxicity (*J Neurosci.* 1992; 12:376-389), and AD patients have an increased incidence of seizures, we asked whether SIRT3 might stabilize neuronal network activity and thereby enable normal cognition even as Aβ accumulates. To this end, we are evaluating behavioral phenotypes and cellular and molecular alterations in brain neuronal networks in $SIRT3^{-/-}$ mice and APP/PS1 double mutant transgenic mice with a SIRT3 haploinsufficiency. We find that SIRT3 is required for adaptation of hippocampal and amygdala neuronal network activity (up-regulation of GABAergic tone) to bioenergetic/excitatory challenges (intermittent food deprivation and exposure to picrotoxin) in non-AD mice. While APP/PS1 AD mice have a propensity to develop seizures, APP/PS1 SIRT3+/- mice exhibit severe seizures and die between the ages of 3 and 6 months. We are determining whether APP/PS1 SIRT3+/- mice have accelerated behavioral and neuropathological phenotypes, and whether increasing SIRT3 expression in hippocampal neurons using AAV-mediated gene therapy will ameliorate neuronal network abnormalities and cognitive impairment in APP/PS1 AD mice. Supported by the NIA Intramural Research Program.

**Disclosures:** **N.R. Ghena:** None. **Y. Liu:** None. **A. Cheng:** None. **M.P. Mattson:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.12/Q2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Altered cortical and hippocampal excitability in TgF344-AD rats modeling Alzheimer’s disease pathology

**Authors: *M. STOILJKOVIC**, C. KELLEY, B. STUTZ, T. L. HORVATH, M. HAJÓS
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**Abstract:** Current neurophysiological findings suggest that accumulation of amyloid-β (Aβ) and hyperphosphorylated tau in the brain disrupt synaptic function in hippocampal-cortical neuronal networks leading to impairment in cognitive and affective functions in Alzheimer’s disease (AD). Available therapies in clinical practice have limited efficacy and do not affect AD progression, while development of new drugs with disease-modifying potential has proven a challenge due in large part to the lack of highly predictive animal models and assays. In the present study we recorded neural activity in TgF344-AD rats, a recently developed transgenic model with a full array of AD pathological features, including age-dependent accumulation and deposition of Aβ, tauopathy, apoptotic neuronal loss, and cognitive impairment (Cohen et al., 2013). Under urethane anesthesia, TgF344-AD rats showed significant age-dependent decline in brainstem-elicited hippocampal theta oscillation and decreased theta-phase-gamma amplitude

coupling comparing to their age-matched WT counterparts. In freely-moving condition, hippocampal and cortical recordings also demonstrated altered neuronal activities. Both the power of hippocampal theta oscillation and gamma power during sharp-wave ripples were significantly lower in TgF344-AD rats. Additionally, these rats showed impaired coherence in both intercortical and hippocampal-cortical network dynamics. Cortical EEG also revealed higher neuronal excitability with increased incidence of paroxysmal hypersynchronous high-voltage spindles, which occur during awake, behaviorally quiescent state. Furthermore, TgF344-AD rats demonstrated impairments in sensory processing, having diminished auditory gating and 40-Hz auditory evoked steady-state response in the auditory cortex. Subsequent analyses of these rats showed accumulation of hyperphosphorylated tau in basal forebrain cholinergic and GABAergic neurons which innervate both the hippocampus and cortex. Also, lower expression of synaptophysin and tenascin-C in hippocampal neurons was present, along with increased levels of key inflammatory cytokines. The observed differences in hippocampal and cortical neurophysiological activity, alterations in synaptic function, and higher inflammatory tone in TgF344-AD rats, which mirror several abnormalities described in AD patients, may be used as promising markers to monitor therapies influencing disease progression.

**Disclosures:** **M. Stoiljkovic:** None. **C. Kelley:** None. **B. Stutz:** None. **T.L. Horvath:** None. **M. Hajós:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.13/Q3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R01 GM083335

NIH Grant R03 AG047132

**Title:** Opposing effects of Aβ42 on cholinergic synaptic activity and a role for synaptic homeostasis

**Authors: *E. HAHM**, R. Y. NAGARAJA, R. TOOKER, S. TSUNODA
Dept Biomed. Sci., Colorado State Univ., Fort Collins, CO

**Abstract:** The generation of β-amyloid (Aβ) peptides in the brain is a primary event leading to Alzheimer’s disease (AD). The toxic Aβ42 species has many effects, including the alteration of neural activity. Interestingly, reported changes include both increases and decreases in neural activity. We find that human Aβ42 induces an increase in cholinergic synaptic activity in *Drosophila*, which is followed by synaptic depression, a sequence of events that parallels

suggested changes in cholinergic activity in mammals. We show that the early increase in synaptic activity is likely due to extracellular Aβ42 acting on pre-synaptic α7 nAChRs, and that increasing synaptic activity can induce a homeostatic decrease in activity at later stages. Conversely, countering the early increase in synaptic activity in Aβ42-expressing cultures prevents the induction of later synaptic depression. Our findings support the hypothesis that endogenous synaptic homeostasis mechanisms are likely to play a key role in the progressive effects of Aβ42 on neurons.

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**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.14/Q4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Supported by Fondecyt 1140473

Beca Conicyt de Doctorado

**Title:** Intracellular Abeta oligomers increase AMPA neurotransmission by pre and postsynaptic actions

**Authors: *L. G. AGUAYO**[1], C. PETERS[2], J. GONZALEZ[2], N. O. RIFFO[2], B. MUÑOZ[2], E. J. FERNANDEZ[2]
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**Abstract:** Introduction
The current dogma of the amyloid cascade supports the conclusion that Aβ interaction with extracellular components of the neuronal membrane initiates neurotoxicity. However, the effect that intracellular Aβ may have on neuronal functions has still not been extensively examined. The presence of intraneuronal Aβ aggregates has been correlated with neuronal death in transgenic mice models, and neurons undergoing degeneration in 5xTg-AD mice showed intracellular amyloid deposits. In this study, we examined the effects of intracellular Aβ oligomers (Aβo) on mice hippocampal neurons from slices and in tissue culture.
Results
Electrophysiological recordings were done using the whole-cell variation of the patch clamp technique in presence of an external solution containing high NaCl and 10 HEPES (pH 7.4). The internal solution consisted of high KCl, ATP-Na2, BAPTA and Aβo oligomers or fibers (5-1000 nM). The holding potential was -60 mV and currents were acquired at 50 μs intervals. $A\beta_{1-42}$ and $A\beta_{1-40}$ were dissolved in HFIP (10 mg/ml) and stored in aliquots at -20ºC. In order to form Aβo,

the samples were stirred at 500 rpm using a Teflon-coated micro-stir bar for 24-48 h at ~22°C and stored at 4°C until required.
The effects of intracellular Aβo were studied on the amplitude, frequency and time course of miniature synaptic currents. Under control conditions, the average frequency of synaptic currents was approximately 0.15±0.02 Hz and increased to 0.67±0.1 Hz after application of 5 nM of Aβ oligomers (5 min). With higher concentrations (50 nM), the effect was faster and larger supporting a concentration dependent effect. Application of denatured Aβ and DMSO did not produce any affects on the frequency of synaptic currents. The effect of Aβ was more selective for oligomers since application of different concentrations of fibrillar Aβ was less active, affecting the frequency of synaptic currents only when applied at 1 μM (0.55±0.2 Hz). The effects of Aβo were more extensive on AMPA-mediated neurotransmission than in $GABA_A$-mediated. The properties of the action potential and the value of the resting membrane potentials were unchanged by the intracellular perfusion of Aβo.
Conclusion
The data showed that low concentrations of intracellular Aβo had a profound effect on synaptic transmission. The effect was more evident on excitatory neurotransmission affecting pre and postsynaptic mechanisms.

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**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.15/Q5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Pomona College Faculty Research Grant

**Title:** The acylated tripeptide Arg-Glu-Arg enhances hippocampal LTP and can reverse LTP deficits produced by $Abeta_{25-35}$

**Authors: *K. D. PARFITT**[1], S. F. WAKE[2], J. C. NECARSULMER[2], V. SRINIVASAN[2], I. SOLOMON[2], K. M. KNOX[2], S. A. CRAWFORD[2], D. J. O'LEARY[3], W. C. ABRAHAM[4]
[1]Dept of Neurosci., Claremont, CA; [2]Dept of Neurosci., [3]Dept of Chem., Pomona Col., Claremont, CA; [4]Psychology, Univ. of Otago, Dunedin, New Zealand

**Abstract:** Secreted APPα (sAPPα), a 612-residue protein derived from amyloid precursor protein, has neurotrophic and neuroprotective properties and enhances hippocampal long term potentiation (LTP) *in vivo* and *in vitro*. Few of the cellular mechanisms of action of sAPPa are known, but a tripeptide sequence within sAPPa—arginine-glutamate-arginine (RER)—has been

proposed as an active region of the protein that enhances memory in a passive-avoidance task in chicks. This tripeptide corresponds to a growth-promoting region of the external domain of APP (amino acids 328-330), can be administered peripherally and seems to cross the blood brain barrier in chicks. We examined the ability of congeners of sAPPα's RER motif, in an acylated and diastereomeric form (Ac-rER), to mimic the LTP-enhancing effects of full-length sAPPα observed previously in rat and mouse hippocampus. First we tested the ability of Ac-rER to enhance LTP induced by mild theta burst stimulation (TBS). Hippocampal slices were prepared from adult male C57Bl/6N mice and allowed to recover for 2 h. Baseline field excitatory postsynaptic potentials (EPSPs) were evoked in area CA1 by electrical stimulation of the Schaffer collateral/commissural pathway, and recorded in stratum radiatum. Application of mild theta-burst stimulation (TBS, 5 trains (5 Hz) of 5 pulses (100 Hz)) induced post-titanic potentiation (PTP) but not LTP in untreated slices. In contrast, when applied 25 min before, during and following the mild TBS, Ac-rER (10 nM) facilitated both PTP and LTP compared to controls (responses 1h post-TBS = 139 ± 4.3 % vs 108 ± 3.1% of baseline; N = 9 and 8, respectively; $p<0.01$). Ac-rER was more effective than the non-diastereomeric peptide (Ac-RER) in enhancing LTP; in the presence of Ac-RER, LTP was 119 ± 6.4 % of baseline. Neither of these tripeptides, nor the randomly selected control Ac-IFR tripeptide, were found to alter baseline synaptic transmission or paired pulse facilitation. To determine whether sAPPα has metaplastic properties, we washed the Ac-rER (10 nM, 30 min) out of the bath for 30 min prior to TBS. Under these conditions, LTP was 125 ± 4% of baseline (vs 108 ± 5% in controls; $p<0.01$). We also examined whether Ac-rER can ameliorate $A\beta_{25-35}$-induced deficits in LTP induced by 3 X TBS (10 trains (5 Hz) of 5 pulses (100 Hz)). Treatment of slices with Ac-rER prior to and during application of $A\beta_{25-35}$ (200 nM) prevented the deficits in LTP observed in the presence of $A\beta_{25-35}$ alone. These results suggest that this acylated diastereomeric tripeptide shares similar plasticity-enhancing properties of sAPPα and has the potential to reverse the deficits in synaptic plasticity seen in Alzheimer's disease.

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**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.16/Q6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Alzheimer's Association (ZEN-15-321663)

**Title:** Synaptology of the mesial temporal cortex in Alzheimer's disease

**Authors: *J. DEFELIPE**[1,2], M. DOMINGUEZ-ALVARO[2], M. MONTERO-CRESPO[1,2], R. INSAUSTI[3], L. BLAZQUEZ-LLORCA[4], L. ALONSO-NANCLARES[1,2]
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**Abstract:** Alzheimer's disease (AD) is the main cause of dementia, accounting for 60-80% of all cases. During the course of the disease, three main neuropathological alterations occur: cerebral atrophy, intracellular neurofibrillary tangles and extracellular amyloid plaques. Early loss of episodic memory in AD patients is closely associated with the progressive degeneration of medial temporal lobe structures, including the hippocampal formation and adjacent cortex. In addition, neurofibrilar tangles are first observed in the transentorhinal (TEC), entorhinal cortex and hippocampal CA1 field. Synapse loss has also been reported, but relatively few detailed studies have been performed using electron microscopy. This is important because elucidation of the changes that affect synapses is crucial for better understanding the pathogenic mechanisms underlying AD. Brain tissue from 5 AD patients and 6 control subjects with no neurological alterations were used in this study. These human brain samples had less than 3h postmortem delays. A 3D ultrastructural analysis of the neuropil in layer II of the TEC and superficial pyramidal layer of the medial CA1 was performed. We used an instrument that combines a high-resolution field-emission SEM column with a focused gallium ion beam (FIB), which mills the sample surface on a nanometer scale. The sequential and automated use of FIB milling and SEM imaging allows us to obtain large image stacks that represent a three-dimensional sample. Customized analysis software was used for the reconstruction of synapses, which allowed their number, morphology (surface area of the synaptic apposition surface) and spatial distribution to be calculated. These spatial and morphological data are of great interest in terms of synaptic function. Our preliminary results show that the total number of synapses per volume in AD patients was lower than in controls, both in CA1 and TEC. However, we have not found differences in the morphology of the synapses in AD patients compared with control subjects. Furthermore, the spatial organization of synapses showed a nearly random 3D distribution, regardless of the subject group and the region analyzed. In conclusion, these data show a decrease in the density of synapses in these brain regions in AD patients but both the spatial distribution and size of the synapses remain unchanged. Further studies will be performed to extend these observations to other brain areas of AD patients and to try to elucidate the functional consequences of these synaptic changes.

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**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.17/Q7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Canadian Institute of Health Research

**Title:** Sigma-1 receptor and sex specificity in a mouse model of Alzheimer's disease

**Authors: *M. A. SNYDER**[1], K. MCCANN[2], E. HRISTOVA[2], R. BERGERON[1,2]
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**Abstract: Background:** Studies suggest that nearly 2/3 of Alzheimer's disease (AD) patients are women and that they have a faster disease progression than men. Despite this clinical profile, only a small fraction of research includes animals of both sexes and even fewer examine data for potential sex differences. With no cure and few treatments available for AD, novel therapeutic targets are desperately needed. One protein of interest is the sigma-1 receptor (Sig1R) which has roles in regulating $Ca^{2+}$ homeostasis, synaptic transmission, cognition, and is modulated by sex hormones. Sig1R agonists are neuroprotective and anti-amnesic in AD models making it a target for intervention. Further, Sig1R binding sites are decreased in post-mortem AD brains and a Sig1R gene polymorphism is a risk factor for AD. Therefore, Sig1R loss could contribute to AD progression. Our research focuses on how amyloid beta (Aβ) induces changes in neuronal $Ca^{2+}$ signaling and causes synaptic dysfunction in the hippocampus. We also evaluate how Sig1R loss contributes to the deficits in AD. **Methods:** We used the well-characterized $A\beta_{25-35}$ infusion AD model, as this paradigm recapitulates the process of sporadic AD. $A\beta_{25-35}$ was infused, *i.c.v.*, into brains of adult male and ovariectomized female wild-type (WT) or Sig1R knockout (KO) mice. Using electrophysiological recording and western blot, we examined Aβ-induced changes to synaptic transmission and synaptic proteins. **Results:** We found that female mice infused with $A\beta_{25-35}$ had an increased post-burst afterhyperpolarization, a paradigm used as a proxy for changes in $Ca^{2+}$ homeostasis. They also had an increased facilitation in response to trains of stimuli. Interestingly, Aβ-infused male mice did not show these changes. Instead, Aβ-infused male mice had alterations in their AMPA/NMDA ratio which was not found in female WT mice but was present in female Sig1RKO mice. Despite these Aβ-induced sex differences in hippocampal function, both male and female Aβ-treated mice had reduced magnitude of long-term potentiation. Surprisingly, Sig1R loss did not exacerbate most Aβ-induced deficits. However, uninfused aged Sig1RKO male and female mice had increased levels of $A\beta_{1-42}$ in their cortex compared to WT mice, suggesting Sig1R loss may interact with aging to increase AD pathology. **Conclusions:** Our data suggest that the mechanistic action of Aβ differs between male and female mice. Understanding how Aβ impacts synaptic function and $Ca^{2+}$ homeostasis

within the male and female hippocampus differently could explain the faster disease progression in females and lead to sex-specific therapeutic intervention.

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**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.18/Q8

**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:** Cargo-specific dynamics of neuronal intracellular transport (NIT)

**Authors:** ***M. FEOLE**, V. M. POZO DEVOTO, M. CARNA, V. LACOVICH, K. TEXLOVA, G. STOKIN
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**Abstract:** The neuronal intracellular transport (NIT) is a highly regulated process, involving several proteins that regulate the trafficking of molecules. Transported proteins are involved in several processes such as synaptic plasticity, neurotransmission, cell morphology, differentiation, cell-cell interaction, degradation and damage signaling. This is particularly relevant during aging when changes in energy metabolism together with oxidative stress, erode the axonal structure and function. Intriguingly, several neurodegenerative disorders, in particular those associated with aging, such as Alzheimer’s disease, exhibit significant axonal pathology including impairments in transport. However, the mechanisms underlying axonal pathology remain poorly elucidated. We aim to characterize transport dynamics of specific cargoes analyzing differences in directionality (anterograde vs retrograde), localization (soma, dendrites, axon) and velocity (fast or slow). For this study a well characterized neuronal culture differentiated from human Neural Stem Cells was used to investigate transport of different cargoes. NIT was investigated using differently transported GFP coupled cargoes, and assessed by live imaging with a confocal microscope. In addition to identify different neuronal compartments immunocytochemistry was performed after imaging. A detailed characterization of transport dynamics from typical proteins (Synaptophysin, BDNF, PSD95, Neurofilaments, etc.) present in different neuronal compartments was obtained. This characterization includes dynamics parameters such as mean velocity, proportion of anterograde/retrograde/stationary movement, segmental velocity, average run length, pauses, and reversions. Preliminary results compared to already elucidated APP transport showed different velocities of various retrograde/anterograde associated cargoes along

the different neuronal compartment. Further experiments will shed light on the intricate NIT network and ultimately provide critical knowledge and its involvement in the pathophysiology of neurodegenerative disorders.

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**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.19/Q9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** National Natural Sciences Foundation of China (No.81473200)

**Title:** L-3-n-butylphthalide rescues hippocampal synaptic failure and attenuates neuropathology in aged app/ps1 mouse model of alzheimer’s disease

**Authors: *Y. PENG**
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**Abstract:** Alzheimer’s disease (AD) is an age-related and irreversibly progressive neurodegenerative disorder that occurs gradually and results in memory, behavior and personality changes. Our previous studies showed that L-3-n-butylphthalide (L-NBP), an extract from seeds of Apium graveolens Linn (Chinese celery), improved cognitive ability in animal models of cerebral ischemia, vascular dementia and AD. It is well known that cognitive deficit of AD is caused by synaptic dysfunction. In this study, we investigated the effect of L-NBP on hippocampal synaptic function in aged APP/PS1 AD transgenic mice and related mechanisms. Eighteen-month-old APP/PS1 transgenic (Tg) mice were administered 15 mg/kg L-NBP by oral gavage for 3 months. Synaptic morphology and the thickness of post-synaptic density (PSD) in hippocampal neurons were investigated by electron microscope. The dendritic spines, Aβ plaques and glia activation were detected by staining. The expressions of synapse-related proteins were observed by western blotting. The results showed that L-NBP treatment significantly increased the number of synapses and apical dendriticthorns and the thickness of PSD, increased the expression levels of synapse-associated proteins including PSD95, synaptophysin (SYN), β-catenin and GSK-3β, and attenuated Aβ plaques and neuroinflammatory responses in aged APP/PS1 Tg mice. It indicated that L-NBP might restore synaptic and spine function in aged APP Tg mice through inhibiting Aβ plaques deposition and neuroinflammtory response. Wnt/β-catenin signaling pathway might be involved in L-NBP-related restoration of synaptic function.

**Disclosures:** **Y. Peng:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.20/Q10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** the Research Grants Council of Hong Kong SAR (16102715 and 16102815)

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**Title:** Activation of the melanocortin 4 receptor signaling pathway ameliorates Alzheimer's disease-like pathology

**Authors: M. TIAN**[1,2,3,4], Y. SHEN[1,2,3,4], *A.-Y. FU[1,2,3,4], N. IP[1,2,3,4]
[1]Div. of Life Sci., The Hong Kong Univ. of Sci. and Technol., Hong Kong, China; [2]Mol. Neurosci. Ctr., The Hong Kong Univ. of Sci. and Technol., China; [3]State Key Lab. of Mol. Neurosci., The Hong Kong Univ. of Sci. and Technol., China; [4]Guangdong Key Lab. of Brain Science, Dis. and Drug Develop., HKUST Shenzhen Research Institute, Shenzhen, China

**Abstract:** One of the pathological hallmarks of Alzheimer’s disease is the deposition of amyloid plaques due to the accumulation of extracellular amyloid-beta (Aβ) peptides. Emerging evidence suggests that the soluble oligomeric form of Aβ is a synaptotoxic agent that mediates the impairment of synaptic functions and disrupts neuronal circuit activities. Meanwhile, hyperactivation of neuronal activity contributes to the overproduction of Aβ. We previously demonstrated that a G protein-coupled receptor, melanocortin 4 receptor (MC4R) is critical for hippocampal synaptic plasticity. Importantly, deregulation of hippocampal MC4R signaling results in the impairment of synaptic plasticity, i.e., long-term potentiation, in Alzheimer’s disease. Suppression of postsynaptic MC4R in the hippocampus exacerbates long-term potentiation deficit in APP/PS1 mice, a transgenic mouse model of Alzheimer’s disease, whereas restoration of MC4R signaling alleviates this hippocampal synaptic plasticity impairment. Here, we demonstrated that specific activation of MC4R results in reduced amyloid pathology. Specifically, intracerebroventricular delivery of the MC4R agonist D-Tyr MTII into the brains of APP/PS1 mice significantly reduced Aβ content. It is interesting to examine whether MC4R signaling reduces Aβ pathology is dependent on the restoration of synaptic functions and circuit activity. Together, our findings suggest that activation of hippocampal MC4R signaling may be a

therapeutic approach for Alzheimer's disease, as indicated by its beneficial effects on impaired synaptic functions and Alzheimer's disease-like pathology.

**Disclosures:** **M. Tian:** None. **Y. Shen:** None. **A. Fu:** None. **N. Ip:** None.

**Poster**

**477. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 477.21/Q11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** A new mechanism of Alzheimer's disease: $GABA_A$ receptor dysfunction induced neuronal hyperactivity

**Authors:** ***D. BI**[1,2], F. GAO[1,2], L. WEN[1], H. BAO[1], Z. WU[1], Y. SHEN[1,2,3,4]
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**Abstract:** β-secretase (BACE1), the rate-limit enzyme of Aβ production, is significantly elevated in the cortex and hippocampus with Alzheimer's disease (AD) brain, which is often accompanied by hyperactive neurons. However, it remains unknown whether elevated BACE1 activity contributes to the hyperactivity of neurons in the AD brain. $GABA_A$ receptor, in general, produces inhibitory currents to prevent neurons from over excitability. We hypothesize that elevated BACE1 activity causes dysfunction of $GABA_A$ receptor, which in turn, leads to hyperactivity of neurons in the AD brain. We used multiple techniques, including co-IP, western blotting, and patch-clamp to address whether BACE1 suppressed the expression and functions of $GABA_A$ receptors. Our preliminary results showed that BACE1 significantly decreased expression level and whole-cell currents of $GABA_A$ receptors in HEK293T cells, suggesting BACE1 modulated $GABA_A$ receptors in vitro. We also used the newly developed mouse model BACE1 transgenic mice in our lab: hubc-BACE1 (HUBC) and also BACE1 knock-out mouse ($BACE^{-/-}$) to investigate whether BACE1 inhibited $GABA_A$ receptor currents in hippocampal neurons in acute brain slices. We found that both phasic and tonic currents of $GABA_A$ receptors were significantly decreased in the dentate gyrus granule cells of HUBC mice and, on the contratry, increased $GABA_A$ receptors were identified in that of $BACE1^{-/-}$ mice. The finding suggested that BACE1 modulated expression and/or functions of $GABA_A$ receptors in vivo. Moreover, we used the Barnes Maze test, to study whether elevated BACE1 activity in mice impaired learning and memory. Compared to wildtype mice, HUBC mice showed decreased long-term potentiation (LTP) in the perforant pathway and impaired spatial memory, suggesting elevated BACE1 impaired cognitive functions.

In summary, our results show that elevated BACE1 activity may be critically involved in hyperexcitation and cognitive impairments in AD by directly inhibiting GABAergic system functions. This would be the first time to identify the regulatory effects of BACE1 on synaptic plasticity and will provide a new potential therapeutic target for AD.

**Disclosures: D. Bi:** None. **F. Gao:** None. **L. Wen:** None. **H. Bao:** None. **Z. Wu:** None. **Y. Shen:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.01/Q12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA Grant AG029777

NIH/NIA Grant AG053150

**Title:** *In vivo* efficacy study of a small molecule inhibitor of tau oligomer formation in htau mice

**Authors: *J. G. MOE**[1], P. K. KRISHNAMURTHY[1], H. JIMENEZ[2], C. GLUCHOWSKI[3], M. E. MCDONNELL[4], A. B. REITZ[4], P. DAVIES[2], E. J. DAVIDOWITZ[1]
[1]Oligomerix, Inc., New York, NY; [2]The Feinstein Inst. for Med. Res., Manhasset, NY; [3]LifeScience Innovations LLC, Danville, CA; [4]Fox Chase Chem. Diversity Center, Inc., Doylestown, PA

**Abstract:** Alzheimer’s disease (AD) progression is associated with the spread of tau pathological aggregates within the brain in a highly reproducible pattern that is used to stage the disease. We have shown that extracellular tau oligomers are cytotoxic to neurons, inhibit long-term potentiation and impair memory formation in mice. Tau oligomers have also been shown to transmit tau pathology to neighboring neurons by seeding tau misfolding and aggregation. Our small molecule approach aims to inhibit intracellular tau oligomer formation to reduce toxicity and to inhibit the spread of tau pathology, whereas other approaches have focused on using immunotherapy to block the extracellular transmission of tau pathology without addressing the continual formation of new tau oligomer seeds within neurons.
We have developed novel assays to select and optimize small molecules inhibiting tau self-association into oligomers to block the aggregation pathway at its start which differentiates our approach from tau fibril formation inhibitor programs. Our proprietary small molecule leads were designed, prepared and optimized to have CNS drug-like properties. Pharmacokinetic studies were performed in mice and showed both good exposure and half-life in the brain. An optimized compound from our lead series was selected for in vivo evaluation in a 5-day toxicity

study in mice at 100 mg/kg p.o. and no adverse events were observed.
A blinded efficacy study was performed in the htau model, best representing the development of tau pathology in AD. Male and female mice (n=100) were separated into four groups and treated for four months starting at three months of age with vehicle, 10 mg/kg, 40 mg/kg or 100 mg/kg of the lead compound milled into feed. All mice survived until the study end point and did not show any adverse events or an inability to thrive. For example, mice in all treatment groups gained weight at the same rates. At the end of the period, mice were sacrificed and their brains collected for histological and biochemical analyses that are in progress. The primary endpoint for the study is statistically significant reduction in insoluble tau, and the secondary endpoints are dose dependent reduction in tau aggregates, reduction in soluble tau, and reduction in phosphorylated tau. The findings of this study will be presented in due course.

**Disclosures:** **J.G. Moe:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **P.K. Krishnamurthy:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc.. **H. Jimenez:** None. **C. Gluchowski:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc.. F. Consulting Fees (e.g., advisory boards); Oligomerix, Inc. **M.E. McDonnell:** 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.; Oligomerix, Inc. **A.B. Reitz:** 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.; Oligomerix, Inc. **P. Davies:** 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.; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc.. F. Consulting Fees (e.g., advisory boards); Oligomerix, Inc. **E.J. Davidowitz:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix.inc..

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.02/R1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** A novel domain receptor inhibitor reduces neuropathology and improves cognition in neurodegenerative models

**Authors: *M. HEBRON**, M. PEYTON, X. LIU, X. GAO, R. WANG, I. LONSKAYA, C. MOUSSA
Georgetown Univ., Washington, DC

**Abstract:** The role of cell surface tyrosine kinase collagen-activated receptors known as discoidin domain receptors (DDR1/2) is unknown in neurodegenerative diseases. We detect up-regulation in the expression level of DDRs in post-mortem Alzheimer and Parkinson brains. It is currently unknown whether regulation of DDRs that modulate many cellular functions is beneficial or detrimental in neurodegeneration. We used lentiviral gene transfer to knockdown DDR1/2 in models of Alzheimer's and Parkinson's disease and determined the effects of DDR receptor level on accumulation of α-synuclein, tau and β-amyloid. We found that DDR knockdown reduces the levels of these proteins and prevents cell loss. DDR knockdown alters brain immunity and significantly reduces the level of triggering receptor expressed on myeloid cells (TREM)-2 and microglia. We used a novel compound called LCB-03-0110 that inhibits DDRs and found significantly reduced levels of neurotoxic proteins, decreased cell death and behavioral improvement in neurodegeneration models. These studies suggest that DDR inhibition is a novel target to clear neurotoxic proteins and reduce inflammation in neurodegeneration. LCB-03-0110 is a pharmacological candidate to treat neurodegenerative diseases.

**Disclosures: M. Hebron:** None. **M. Peyton:** None. **X. Liu:** None. **X. Gao:** None. **R. wang:** None. **I. Lonskaya:** None. **C. Moussa:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.03/R2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** *Ex vivo* autoradiography of GLP-1 receptors in mice

**Authors: *M. MORIN**[1], E. SHER[2], M. P. JOHNSON[1]
[1]Neurosci. Discovery Res., Eli Lilly and Co., Indianapolis, IN; [2]Neurosci. Discovery Res., Eli Lilly and Co., Windlesham, United Kingdom

**Abstract:** Activation of Glucagon-Like Peptide receptors (GLP-1r), critical for glucose metabolism, has been shown to have neuro-protective and anti-inflammatory properties *in vitro* and *in vivo*. In several preclinical models of Alzheimer's disease, peripheral administration of a

GLP-1r agonist has been reported to reduce abnormal neuropathology and improve the cognitive and motor deficits that occur in these models (Brain Research 1634:158-170; Neuromol Med 15:102-114). The exact mechanism by which this occurs is currently unknown, as existing GLP-1r agonists are all large molecule proteins with a theoretically limited ability to cross the blood brain barrier (BBB). In these experiments, an *ex vivo* autoradiography assay was developed to assess the central exposure of peripherally administered GLP-1 receptor agonists in mice. Autoradiography with [$^{125}$I] GLP-1(7-36) was used to determine GLP1-receptor distribution in C57Bl/6 mouse brain and several peripheral tissues under equilibrium conditions. Consistent with the literature, GLP-1(7-36) binding was widely distributed throughout the brain, with the highest levels seen in the lateral septum, habenula and dentate gyrus of the hippocampus. Moderate levels were present in several hypothalamic nuclei (arcuate nucleus, lateral hypothalamus) and the pretectal nucleus of the thalamus. The highest level of GLP-1(7-36) binding in the assessed peripheral tissues was found in the lung. For the *ex vivo* assay, the lateral septal area of the brain and one peripheral tissue (lung) were assessed following subcutaneous dosing of a GLP-1r agonist, liraglutide. Liraglutide (1mg/kg) significantly displaced the [$^{125}$I] GLP-1(7-36) binding in the lung at 2 and 6 hours (63 and 90% inhibition, respectively). However, there was no inhibition of the GLP-1r binding in the lateral septum of the brain. These results may indicative that the neuro-protective effects of GLP-1 agonists are due to an indirect action of GLP-1 activation on neurons, local activation of GLP-1r in a discreet brain region that was not quantified or a low percent occupancy with central GLP-1 receptors that is less than the level of detection of the assay.

**Disclosures:** **M. Morin:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **E. Sher:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **M.P. Johnson:** A. Employment/Salary (full or part-time):; Eli Lilly and Company.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.04/R3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** National Institutes of Health (NIH) 1R01EY023173

NIH 1DP1NS087724

JPB Foundation

Belfer Neurodegeneration Consortium

Halis Family Foundation

NIH RF1 AG047661

**Title:** Gamma frequency entertainment ameliorates AD-associated pathology and transforms microglia in AD mouse models

**Authors: *A. J. MARTORELL**[1], D. NAM-WOO KIM[1], A. PAULSON[3], H.-J. SUK[2], A. SINGER[3], L.-H. TSAI[2]
[1]BCS, [2]MIT, Cambridge, MA; [3]Georgia Tech., Atlanta, GA

**Abstract:** Gamma power has been shown to be altered in several neurological diseases, including Alzheimer's disease. Previous work from our lab showed a reduction in gamma power (with a unimodal distribution around 40 Hz) in the 5XFAD mouse model, in young amyloid pre-depositing mice. Using a non-invasive 40 Hz light flicker, we were able to entrain gamma oscillations in the visual cortex, and observed a transformation in microglial morphology and reduction in amyloid load. Here, we investigated whether stimulation of other sensory modalities at 40 Hz, such as auditory, can have an effect on Alzheimer's-like pathology. We applied a 40 Hz auditory stimulation, and observed markedly reduced amyloid load and tau phosphorylation as well as microglia activation in both the auditory cortex and hippocampus. Our data demonstrates a non-invasive strategy to ameliorate AD-like pathology in regions additional to the primary sensory cortex in several AD mouse models.

**Disclosures: A.J. Martorell:** None. **D. Nam-Woo Kim:** None. **A. Paulson:** None. **H. Suk:** None. **A. Singer:** None. **L. Tsai:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.05/R4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Inosine improve cognition in aged rats- Possible antioxidant and anti-inflammatory mechanism

**Authors: *P. RUHAL**, D. DHINGRA
Guru Jambheshwar Univ. of Sci. and Technol., Hisar, India

**Abstract:** Aging is characterized by progressive decline in physiological functions due to maladaptation of synaptic processes that eventually results in aberrant perception, cognitive dysfunction and neurodegeneration. This deterioration is due to the formation of engrams in the brain and one of that is the "oxidative stress" which occurs due to imbalance between the generation of free radicals and antioxidant enzyme activity. As the population is aging, the incidence of age-related neurodegenerative diseases, such as Alzheimer's disease, is growing. In

the present study, we investigated the effect of inosine (50, 100 and 200 mg/kg; i.p.) in 18 months old middle-aged male rats. Inosine was administered to rats for 14 successive days. Donepezil (1mg/kg; i.p.), an acetylcholinesterase inhibitor was used as a standard drug. Behavioural models were used to evaluate the effect of drugs on learning and memory of rats. After behavioural studies, animals were sacrificed for the preparation of cytoplasmic fractions of hippocampus and pre-frontal cortex for the quantification of acetylcholinesterase activity, oxidative stress parameters, proinflammatory marker i.e. TNF-α, IL-6 and histopathological examinations. Inosine significantly improved learning and memory of rats when tested in behavioural models. Further, inosine significantly reduced the oxidative stress markers and improved antioxidant enzyme activities (i.e. SOD and GSH). However, no significant difference in AChEs activity was observed in inosine treated groups in comparison to aged control rats. Further, TNF-α and IL-6 level were found to be ameliorated in ICV-STZ-treated rats after the treatment of inosine in a dose dependent manner. Histopathological evaluation showed that inosine treated aged rats has less number of pyknotic neurons as compared to aged control rats. **Conclusion:** Inosine significantly improved learning and memory of rats possibly through its dual effect i.e. antioxidant as well as anti-inflammatory effect and improvement of neuronal survival in hippocampal CA-1 region of middle-aged rats. However, additional study is needed to further explore the downstream signalling pathways involved in the neuroprotective effect of inosine in aged animals.

**Disclosures: P. Ruhal:** None. **D. Dhingra:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.06/R5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Histone Deacetylase inhibitor, sodium butyrate, exerts neuroprotective actions in intracerebroventricular streptozotocin induced biochemical abnormalities in rats

**Authors: *S. SHARMA**, R. TALIYAN
Birla Inst. of Technol. and Science, Pilani, Pilani, India

**Abstract: Background** Alzheimer’s disease (AD) is the leading cause of dementia and is characterized by progressive loss of memory and other cognitive functions. Both neuro-inflammation and oxidative stress have been reported to be elevated in AD. Recently, reduced histone acetylation along with elevated expression and activity of histone deacetylases (HDACs) has also been reported in various preclinical and clinical studies of AD. Thus, the present study was undertaken to determine the therapeutic potential of HDAC inhibitor, Sodium butyrate (NaB) in Intracerebroventricular-Streptozotocin (ICV-STZ) induced sporadic Alzheimer's

disease (sAD) in rats.
**Methods** Adult Male Wistar rats (250-350g) were infused with STZ twice (3 mg/kg ICV) on alternate days (day 1 and day 3) using following coordinates: 0.8 mm posterior to bregma; 1.5 mm lateral to sagittal suture; 3.6 mm ventral from the surface of the brain. The ICV-STZ treated rats received either vehicle (0.9%w/v NaCl) or NaB (150 and 300mg/kg, i.p.) for a period of 21 days. Thereafter the animals were sacrificed; brains were removed and used for biochemical and histological studies.
**Results** The ICV-STZ administration results in significant elevation of oxidative-nitrosative stress (malondialdehyde and nitrite levels), reduction in antioxidant enzyme level (reduced glutathione), increase of pro-inflammatory marker (Tumour necrosis factor-α) in hippocampus homogenates as compared to vehicle treated animals. In addition, ICV-STZ administration results in reduced level of global histone H3 acetylation and brain derived neurotrophic factor (BDNF) in hippocampus brain homogenate. In contrast, NaB treatment significantly and dose dependently attenuated the oxidative-nitrosative stress and neuro-inflammatory markers in ICV-STZ treated rats. Further, NaB treatment augments the histone H3 acetylation and BDNF levels in ICV-STZ treated rats. Moreover, the neuroprotective effects of NaB were further confirmed by increased neuronal count in hippocampus regions during histological studies.
**Conclusion** The neuroprotective effects of NaB may be due to its ability to attenuate inflammatory markers or its antioxidant potential. Moreover, based upon these results, it could be suggested that HDAC inhibitors might exert neuroprotective actions by increasing H3 acetylation and subsequently BDNF levels.

**Disclosures: S. Sharma:** None. **R. Taliyan:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.07/R6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA extramural Grant 1R25AG047843-01

**Title:** Effects of metformin in combination with voluntary exercise in a female transgenic mouse model of Alzheimer's Disease

**Authors: A. JALDI**, F. BELLO, T. SMITH, T. FALEGAN, *J. S. ALLARD
Physiol. and Biophysics, Howard Univ. Col. of Med., Washington, DC

**Abstract:** Type-2 diabetes (T2DM) presents a 1.5 to 2-fold increased risk for Alzheimer’s disease (AD). Researchers are focused on the role of neuronal insulin resistance as a potential cause. If true, then insulin-sensitizing agents may be effective therapies for both peripheral and

central insulin resistance. Both metformin treatment and aerobic exercise have powerful anti-diabetic effects, including insulin-sensitization. The overall goal of this study is to understand the impact and mechanisms by which metformin treatment and voluntary exercise affect brain function, neuronal insulin signaling and the progression of neurodegenerative disease. Using the APP/PS1 mouse model of AD, the effects of metformin and exercise therapy separately, alone and in conjunction are compared. Metformin intake was approximated at a daily dose of 70 mg/kg body weight for one year and animals had free access to an in-cage running wheel. AD pathology in the adult mouse brain, including inflammation and amyloid beta plaque deposition are analyzed, as well as glucose metabolism. These results provide new information on the effects of metformin in combination with exercise on AD-like pathology.

**Disclosures:** **A. Jaldi:** None. **F. Bello:** None. **T. Smith:** None. **T. Falegan:** None. **J.S. Allard:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.08/R7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** SORBI ECRF15

**Title:** Hydroxytyrosol protects TgCRND8 mice against Aβ toxicity

**Authors: P. NARDIELLO**[1], D. PANTANO[1], M. STEFANI[2], *M. MEMO[3], F. CASAMENTI[1]
[1]Dept. of Neuroscience, Psychology, Drug Res. and Child Health, Div., [2]Dept. of Biomedical, Exptl. and Clin. Sci. “Mario Serio”, Univ. of Florence, Florence, Italy; [3]Univ. of Brescia, Brescia, Italy

**Abstract:** The overall health beneficial effects of extra virgin olive oil (EVOO) phenolic components are well established. Our previous data have shown the protection of oleuropein aglycone (OLE) against protein/peptide aggregation *in vitro* and in TgCRND8 mice, a transgenic model of Aβ deposition. A protective action of the oral intake of a mix of polyphenols present in olive mill waste water was also shown. Here we extended our previous investigations on the neuroprotective, antinflammatory and antioxidant power of EVOO polyphenols by investigating the effects on cognitive functions, brain amyloid deposits, neuroinflammation and oxidative stress in TgCRND8 mice following diet supplementation with hydroxytyrosol (HT), a major polyphenol in olive oil and the main metabolite of oleuropein aglycone.
4-month-old Tg mice (n=6/group/genotype, equally divided for sex) were used for treatment. The animals were fed for 8 weeks with a modified low-fat (5.0%) AIN-76A diet (10 g/day per mouse) supplemented with HT (50 mg/kg of diet). The animals were divided into four different

groups: i) Tg mice fed with low-fat diet as such (untreated Tg mice); ii) Tg mice fed with the same diet supplemented with HT (HT-fed Tg mice); iii) wt mice fed with low-fat diet as such (untreated wt mice); iv) wt mice fed with the same diet supplemented with HT (HT-fed wt mice). Behavioral performance was evaluated by means of Morris Water Maze, step down inhibitory avoidance and object recognition tests. Neuropathological investigations were carried out by immunohistochemistry and western blotting analysis. We found that dietary supplementation with HT significantly improves cognitive performances of Tg mice respect to untreated Tg mice. Similar to data reported for OLE, we found that HT administration to these mice triggers autophagy in the cortex and reduces the accumulation of amyloid aggregates of Aβ42 and its pyroglutamylated 3–42 derivative (pE3-Aβ) in the cortex and hippocampus, as compared to untreated Tg mice. HT administration also affected the inflammatory response in the hippocampal areas, as shown by the reduced astrocytes activation and TNF-α mRNA levels. These results support HT neuroprotection *in vivo* against Aβ toxicity and its involvement in the beneficial effects of the Mediterranean diet for Alzheimer‘s disease prevention.

**Disclosures: P. Nardiello:** None. **D. Pantano:** None. **M. Stefani:** None. **M. Memo:** None. **F. Casamenti:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.09/R8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH 5R01AG048993

**Title:** Modulation of IGF-1R ameliorates Alzheimer's disease phenotype in a transgenic mouse model

**Authors:** *M. SOHRABI, ***M. SOHRABI**, G. D. MANOCHA, C. COMBS
Biomed. Sci., Univ. of North Dakota, Grand Forks, ND

**Abstract:** Alzheimer’s disease (AD) is characterized by extracellular amyloid β (Aβ) peptide accumulation and intracellular neurofibrillary tangles. Aging is a major risk factor for development of this progressive neurodegenerative disorder. Insulin like growth factor-1 (IGF-1), upon binding to its receptor (IGF-1R), regulates growth, development, aging, and lifespan. However, the contribution of this growth factor to age-related AD pathology and progression is highly controversial. Based on our previous work, APP/PS1 double transgenic mice demonstrated a decrease in brain IGF-1 levels when they were crossed with Ames dwarf mice (df/df). Subsequently, a reduction in gliosis, Aβ plaque deposition, and Aβ 1-40/42 concentrations were observed in this mouse model. This correlation supported the hypothesis

that IGF-1 may contribute to progression of disease. To better assess the role of IGF-1 in AD, 9-10 month-old male littermate control wild type and APP/PS1 mice were randomly divided into 3 treatment groups including control (untreated), vehicle (DMSO), and picropodophyllin (PPP), a potent, selective, competitive, and reversible IGF-1R inhibitor. The brain penetrant, specific inhibitor was dissolved in DMSO and given to the drug-treated mice via ip. injection of 1mg/kg/day. Mice were sacrificed after 7 days of daily injection and the brains and spleens were collected to quantify histologic and biochemical changes. The PPP-treated APP/PS1 mice demonstrated attenuated pro-inflammatory cytokine levels in the temporal cortex including IL-6 and IL-1β. Additionally, insoluble Aβ 1-40, soluble, and insoluble Aβ 1-42 levels, microgliosis, protein phosphotyrosine, and APP levels were reduced due to drug treatment. Our data suggests IGF-1R signaling is associated with disease progression in this mouse model. More importantly, modulation of the IGF-1R signaling pathway in the brain, even in aged animals, is sufficient to reverse disease phenotype. This suggests that small molecule therapy targeting the IGF-1R pathway is viable for late stage disease treatment.

**Disclosures: M. Sohrabi:** None. **G. D. Manocha:** None. **C. Combs:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.10/R9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** IBRO/SfN Award

**Title:** Abeta oligomers mediate proteasome inhibition especially at synapse

**Authors: *F. CAMPOS RIBEIRO**[1], D. COZACHENCO FERREIRA[2], G. BRAGA[2], J. SATO FORTUNA[2], F. GUARINO DE FELICE[3], S. FERREIRA[4]
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**Abstract:** Accumulation of oligomeric forms of the amyloid beta peptide (AβOs) in specific regions of the brain is thought to be a central cause of synapse damage/loss and cognitive decline in Alzheimer’s disease (DA). Nevertheless, despite being a topic of extensive study, the mechanisms by which AβOs build-up occurs is still a matter of intense debate. The proteasome, the main degradation machinery in the cell, appears to be a central player in AβOs clearance. Further, although there are conflicting results in the literature, it has been reported that Aβ inhibits the proteasome, possibly by binding to the proteasome's catalytic subunits. Here, we report that AβOs at low concentrations inhibit the proteasome in (1) hippocampal neuronal

cultures, (2) synaptosomes extracted from the hippocampi of AβOs-i.c.v.-injected mice and (3) when directly applied to isolated synaptosomes. These results corroborate other studies in the literature regarding proteasome inhibition by Aβ, point to AβOs as a high-affinity proteasome inhibitor, and show that AβOs-mediated proteasome inhibition is even more prominent on synapses. Proteasome inhibition, thus, may be a key event in AD pathology by enabling AβOs levels to rise, setting the stage for neurodegeneration to occur.

**Disclosures: F. Campos Ribeiro:** None. **D. Cozachenco Ferreira:** None. **G. Braga:** None. **J. Sato Fortuna:** None. **F. Guarino de Felice:** None. **S. Ferreira:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.11/R10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Intranasal delivery of Aβ oligomers impairs memory in mice

**Authors: *D. C. MEJIDO**, K. G. N. FERREIRA, H. M. MELO, F. G. DE FELICE
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**Abstract:** Alzheimer's disease (AD) is a neurodegenerative disorder that progressively impairs memory and cognitive functions. Since its first description, myriad studies have been conducted to characterize the complex pathophysiology of this disease, now recognized as the most common type of dementia. AD was initially associated with deposition of fibrillar forms of the amyloid β peptide (Aβ) on the neuronal extracellular surface, as well as the intracellular aggregation of tau protein in neurofibrillary tangles. However, recent evidence support that small soluble Aβ oligomers (AβOs) are central to neurodegeneration in AD. Dysfunctions in synaptic plasticity that lead to memory impairment and culminate in neuronal loss are specifically associated with the neurotoxicity of soluble oligomers. Still, investigators of AD neuropathology often rely on transgenic animal models that do not reflect the direct effects of AβOs, nor resemble the sporadic cases of the disease. Our group has previously validated AD experimental models based on intracerebroventricular (i.c.v.) injection of synthetic AβOs in mice and non-human primates, and applied them to evaluate both synaptic plasticity and memory deficits, as well as the association of metabolic dysfunctions with AD. Investigating the mechanisms by which oligomers affect brain insulin signaling, we demonstrated that AβOs can inhibit insulin receptor substrate (IRS-1) and internalize its receptor in the mouse brain. However, the i.c.v. route for AβO administration imposes some limitations, not being adequate for multiple injections in chronic regimens, nor being easily performed, demanding constant user training and complete anesthesia of the animals. To address these problems and possible biases, here we

propose an alternative approach for AβO administration, using an intranasal (IN) route, which has been considered a promising technique for direct delivery of peptides to the central nervous system, bypassing the blood-brain barrier. We now show that IN delivery of AβOs (500 pmols) in mice significantly impairs short term memory in an object recognition test paradigm, 24 hours, 7 or 21 days after a single administration. These preliminary findings suggest that IN delivery of AβOs produce the same behavioral impacts observed with the well-established i.c.v paradigm. Importantly, same animals impaired by IN oligomers exhibited a trend of decrease in synapse associated proteins PSD-95 and synaptophysin. Therefore, IN delivery of AβOs holds promise as a novel and improved approach for modelling AD in mice; the first to allow the isolated study of AβO toxicity in the brain in a non-invasive manner.

**Disclosures: D.C. Mejido:** None. **K.G.N. Ferreira:** None. **H.M. Melo:** None. **F.G. De Felice:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.12/S1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** CnPQ

FAPERJ

**Title:** Brain infusion of alfa-synuclein oligomers induces motor and non motor Parkinson's Disease-like symptoms in mice

**Authors: *P. DA SILVA FROST**[1], J. TIEMI SATO FORTUNA[6], M. GRALLE[2], D. BECKMAN[7], F. NEVES[6], L. PEREIRA DINIZ[3], F. GOMES DE QUEIROZ BARROS[8], L. E. SANTOS[4], R. GONÇALVES[4], L. ROMÃO[4], D. ZAMBERLAN[9], F. ANTUNES SOARES[9], C. BRAGA[4], D. FOGUEL[4], F. CARVALHO ALCANTÂRA GOMES[3], F. G. DE FELICE[10], S. FERREIRA[6], J. HELENA ROSAURO CLARKE[5], C. P. FIGUEIREDO[11]
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**Abstract:** Parkinson’s disease (PD) is classically characterized by debilitatingmotor symptoms, which are preceded by a number of non-motor symptoms including olfactory deficits, anxiety, depression and cognitive impairment. Aggregation of α-synuclein (alfa-syn), ultimately giving

rise to formation of Lewy bodies in dopaminergic neurons, is thought to play a central role in PDpathology. However, whether amyloid fibrils or pre-fibrillar soluble oligomersof alfa-syn are the main neurotoxic species in PD remains controversial. Here, we investigated the impact of a single intracerebroventricular (i.c.v.) infusion of α-syn oligomers (alfa-SYOs) on motor and non-motor symptoms of PD in mice. alfa-SYOs induced olfactory dysfunction, and decreased dopamine levels and numbers of TH-positive cells in the olfactory bulb, 4 and 8 days post infusion (dpi), respectively. The olfactory deficit persisted until 45 dpi, at which time point olfactory bulb dopamine levels had returned to control levels. alfa-SYO-infused mice had no deficit in object recognition memory, but showed increased anxiety-like behavior 20 dpi. Finally, administration of alfa-SYOs induced late motor impairment and reduction in TH-levels and dopamine content in the striatum 45 dpi. In conclusion, i.c.v. infusion of alfa-SYOs recapitulated PD-associated motor and non-motor symptoms in a temporal sequence similar to that seen in PD patients. Results point to alfa-syn oligomers as the proximal neurotoxins responsible for early non-motor and motor deficits in PD, and suggest that the i.c.v. infusion model characterized here may comprise a useful tool for identification of novel therapeutic targets and for drug screening approaches for PD

**Disclosures:** **P. Da Silva Frost:** None. **J. Tiemi Sato Fortuna:** None. **M. Gralle:** None. **D. Beckman:** None. **F. Neves:** None. **L. Pereira Diniz:** None. **F. Gomes De Queiroz Barros:** None. **L.E. Santos:** None. **R. Gonçalves:** None. **L. Romão:** None. **D. Zamberlan:** None. **F. Antunes Soares:** None. **C. Braga:** None. **D. Foguel:** None. **F. Carvalho Alcantâra Gomes:** None. **F.G. De Felice:** None. **S. Ferreira:** None. **J. Helena Rosauro Clarke:** None. **C.P. Figueiredo:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.13/S2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** PROLAB IBRO

FAPERJ Brazil

CNPq Brazil

CONICET Argentina

**Title:** IGF1 gene transfer protects against Abeta oligomer- induced neuronal damage and memory impairment in mice

**Authors: *M. SELLÉS**[1], M. F. ZAPPA VILLAR[2], P. C. REGGIANI[2], S. FERREIRA[1,3]
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**Abstract:** Alzheimer´s disease (AD) is the main cause of dementia worldwide. Although the prevalence of AD is increasing, there is no effective therapy to treat this neurodegenerative disease. Considerable evidence indicates that soluble oligomers of the amyloid-beta peptide (AβOs), which accumulate in AD brains, are implicated in early synaptic dysfunction and memory impairment in AD. Previously, we have reported that exposure of primary hippocampal neurons to AβOs induces internalization of dendritic insulin receptors (IR) (De Felice et al., 2009, PNAS) and inhibition of insulin receptor substrate-1 (IRS-1) (Bomfim et al., JCI, 2012), inducing neuronal insulin resistance. Insulin plays important roles in neuronal survival, learning and memory, and its possible beneficial effects have been tested in clinical trials for AD. Although insulin appears to improve cognition in control individuals and in early stages of AD, protective effects were not readily observed in late stages of the disease. Possible explanations for this include the removal of IRs from the neural surface instigated by oligomers, and blockade of IR-mediated signaling by AβO-induced IRS-1 inhibition. We have now investigated whether insulin-like growth factor 1 (IGF-1) could be utilized to circumvent IR signaling blockade and to promote alternative activation of insulin-related pathways, thus protecting neurons from AβO-induced damage. We first found that exposure to AβOs did not affect surface levels of IGF-1 receptor in hippocampal neuronal cultures. To test our hypothesis, we employed a recombinant adenoviral vector (Rad-IGF-1) to induce over-expression of IGF-1 in hippocampal cultures for two weeks prior to exposure to AβOs (500 nM). Cultures were then evaluated for neuronal binding of AβOs, synaptic integrity, and neuronal oxidative stress (production of reactive oxygen species, ROS). Interestingly, despite only a slight decrease in AβO binding to neurons, viral-mediated expression of IGF-1 prevented AβO-induced dendritic spine loss and excessive ROS production. Next, we performed intracerebroventricular (i.c.v.) injection of Rad-IGF-1 in Swiss mice two weeks prior to i.c.v. infusion of AβOs, a model we have implemented to study the *in vivo* impact of AβOs (Figueiredo et al., 2012, J. Neurosci.). Interestingly, brain expression of IGF-1 protected against memory impairment induced by AβOs, as assessed using the novel object recognition test. Results suggest that RAd-IGF-1 gene therapy could be a promising strategy to protect neuronal damage and memory impairment induced by AβOs.

**Disclosures: M. Sellés:** None. **M.F. Zappa Villar:** None. **P.C. Reggiani:** None. **S. Ferreira:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.14/S3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** CNPq

CAPES

FAPERJ

INNT

ISN

**Title:** Investigating neuroprotective actions of irisin in the central nervous system

**Authors: *G. B. DE FREITAS**[1], M. V. LOURENCO[2], M. GRALLE[3], S. FERREIRA[4], F. G. DE FELICE[5]
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**Abstract:** Recent studies have indicated that irisin, an exercise-induced myokine first identified as a regulator of adipocyte metabolism, may play important roles in brain function. Irisin was reported to stimulate hippocampal BDNF expression, which, in turn, promotes neuronal survival, synaptic plasticity and memory. However, the mechanisms underlying brain actions of irisin are still unclear. Decrease levels of brain-derived neurotrophic factor (BDNF) and abnormal activation of the unfolded protein response (UPR) have been described to play important roles inducing brain dysfunction in Alzheimer’s disease and other neurodegenerative diseases. Here, we have produced recombinant irisin to test its ability in modulating these signaling pathways. Primary hippocampal cultures were treated with irisin, followed by quantification of the expression of BDNF and of genes related to the UPR. We found that irisin significantly increased BDNF and reduced UPR-related gene expression (ATF4 and CHOP) in hippocampal neurons. Our results support the notion that irisin has neuromodulatory effects in the hippocampus, which could be of relevance to learning and memory processes.

**Disclosures: G.B. De Freitas:** None. **M.V. Lourenco:** None. **M. Gralle:** None. **S. Ferreira:** None. **F.G. De Felice:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.15/S4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** do Rio de Janeiro (FAPERJ)

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)

**Title:** The saturated fatty acid palmitate induces cognitive impairment in mice

**Authors: *H. M. DE MELO**, S. FERREIRA, F. G. DE FELICE
Federal Univ. of Rio De Janeiro, Rio De Janeiro, Brazil

**Abstract:** Obesity is a chronic epidemic disease that affects an increasing number of individuals worldwide and constitutes the most important risk factor for the development of type 2 diabetes mellitus. Obese and type 2 diabetes mellitus humans present structural changes in the brain and cognitive dysfunction. The increase of saturated fatty acids, such as palmitate, in the circulation has been shown to be relevant in the pathogenesis and development of obesity. Brain palmitate uptake is increased in obese patients, and positively correlated with age. Here, we aimed to evaluate the impact of palmitate in the hippocampus, a brain region key for learning and memory. Using *in vivo* intracerebroventricular (icv) injections of palmitate in male Swiss mice, we observed that palmitate induces cognitive impairment in novel object recognition, novel location recognition, step-down inhibitory avoidance and Barnes maze tasks. By using non-radioactive puromycin incorporation assays, we further observed that palmitate attenuates *de novo* protein synthesis in hippocampal slices. Among these proteins, we highlight the reduction of synaptophysin, an important synaptic anchoring protein. Our results imply excessive palmitate levels in the brain as a likely mechanism explaining cognitive impairment in obesity and type 2 diabetes mellitus. Thus, strategies aimed to prevent increased circulating free fatty acids, such as a healthier lifestyle and food, may prevent palmitate-associated effects in obesity, contributing to better cognitive performance and healthy aging.

**Disclosures:** **H.M. De Melo:** None. **S. Ferreira:** None. **F.G. De Felice:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.16/T1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Brain-defective insuling signaling is associated to late cognitive impairment in post-septic mice

**Authors: *D. C. FERREIRA**[1], F. S. NEVES[1], F. BARROS-ARAGÃO[1], J. NUNES[1], A. M. VENANCIO[2], R. L. FROZZA[1], G. F. PASSOS[1], R. COSTA[1], J. DE OLIVEIRA[2], D. F. ENGEL[2], A. F. DE BEM[2], C. F. BENJAMIM[1], F. G. DE FELICE[3], S. T. FERREIRA[1], J. R. CLARKE[1], C. P. FIGUEIREDO[1]
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**Abstract:** Sepsis survivors frequently develop late cognitive impairment. Because little is known of the mechanisms driving this post-septic memory dysfunction, there are no current effective approaches to prevent or treat it. Here, we subjected mice to severe sepsis induced by cecal ligation and puncture (CLP) and evaluated the sepsis-surviving animals in the open field, novel object recognition (NOR), and step-down inhibitory avoidance (IA) task at different times after surgery. Post-septic mice (30 days post-surgery) failed in the NOR and IA tests but exhibited normal performance when re-evaluated 45 days after surgery. Cognitive impairment in post-septic mice was accompanied by reduced hippocampal levels of proteins involved in synaptic plasticity, including synaptophysin, cAMP response element-binding protein (CREB), CREB phosphorylated at serine residue 133 (CREBpSer133), and GluA1 phosphorylated at serine residue 845 (GluA1pSer845). Expression of tumor necrosis factor α (TNF-α) was increased and brain insulin signaling was disrupted, as indicated by increased hippocampal IRS-1 phosphorylation at serine 636 (IRS-1pSer636) and decreased phosphorylation of IRS-1 at tyrosine 465 (IRS-1pTyr465), in the hippocampus 30 days after CLP. Phosphorylation of Akt at serine 473 (AktpSer473) and of GSK3 at serine 9 (GSK3βpSer9) were also decreased in hippocampi of post-septic animals, further indicating that brain insulin signaling is disrupted by sepsis. We also treated post-septic mice with liraglutide, a GLP-1 receptor agonist with insulinotropic activity, or TDZD-8, a GSK3β inhibitor, which rescued NOR memory. In conclusion, these results establish that hippocampal inflammation and disrupted insulin signaling are induced by sepsis and are linked to late memory impairment in sepsis survivors.

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**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** National Institute for Translational Neuroscience

Conselho Nacional de Desenvolvimento Científico e Tecnológico

Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro

Fundação de Amparo à Pesquisa do Estado de São Paulo

CAPES

**Title:** Chronic sleep restriction promotes brain inflammation and synapse loss, and potentiates memory impairment induced by amyloid-β oligomers in mice

**Authors: *G. C. KINCHESKI**[1], I. S. VALENTIM[2], J. R. CLARKE[3], D. COZACHENCO[4], M. T. L. CASTELO-BRANCO[4], A. M. RAMOS-LOBO[5], V. M. B. D. RUMJANEK[4], J. DONATO JR[5], F. G. DE FELICE[4], S. FERREIRA[6]
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**Abstract:** It is increasingly recognized that sleep disturbances and Alzheimer's disease (AD) share a bidirectional relationship. AD patients exhibit sleep problems and alterations in the regulation of circadian rhythms; conversely, poor quality of sleep increases the risk of development of AD. The aim of the current study was to determine whether chronic sleep restriction potentiates the brain impact of amyloid-β oligomers (AβOs), toxins that build up in AD brains and are thought to underlie synapse damage and memory impairment. We further investigated whether alterations in levels of pro-inflammatory mediators could play a role in memory impairment in sleep-restricted male mice. We found that a single intracerebroventricular (i.c.v.) infusion of AβOs disturbed sleep pattern in mice. Conversely, chronically sleep-restricted mice exhibited higher brain expression of pro-inflammatory mediators, reductions in levels of pre- and post-synaptic marker proteins, and exhibited increased susceptibility to the impact of i.c.v. infusion of a sub-toxic dose of AβOs (1 pmol) on performance in the novel object

recognition memory task. Sleep-restricted mice further exhibited an increase in brain TNF-α levels in response to AβOs. Interestingly, memory impairment in sleep-restricted AβO-infused mice was prevented by treatment with the TNF-α neutralizing monoclonal antibody, infliximab. Results substantiate the notion of a dual relationship between sleep and AD, whereby AβOs disrupt sleep/wake patterns and chronic sleep restriction increases brain vulnerability to AβOs, and point to a key role of brain inflammation in increased susceptibility to AβOs in sleep-restricted mice.

**Disclosures: G.C. Kincheski:** None. **I.S. Valentim:** None. **J.R. Clarke:** None. **D. Cozachenco:** None. **M.T.L. Castelo-Branco:** None. **A.M. Ramos-Lobo:** None. **V.M.B.D. Rumjanek:** None. **J. Donato Jr:** None. **F.G. De Felice:** None. **S. Ferreira:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

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**Program#/Poster#:** 478.18/T3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Funding from Srinakharinwirot University

**Title:** Sesamin and sasamolin reduce amyloid-beta toxicity in a transgenic *Caenorhabditis elegans*

**Authors: *R. KEOWKASE**, N. SHOOMAROM, W. BUNARJIN
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**Abstract:** Alzheimer’s disease (AD) is a devastating neurodegenerative disease and is characterized by β-amyloid (Aβ) plaques in the brain. At the present, there is still no approved drug with a proven disease-modifying effect. Sesame seed (*Sesame indicum*) has long been known as a natural healthy food in Southeast Asian countries. Many evidences suggested that sesame lignans including sesamin, sesamolin, and sesamol obtained from sesame seed possess antioxidative property. To test whether these sesame lignans exhibit benefit effects in AD, the transgenic *Caenorhabditis elegans* (*C. elegans*) model of Aβ toxicity was utilized. The purpose of this study was to investigate the protective effect of sesame lignans against Aβ toxicity. Among tested compounds, sesamin and sesamolin significantly delayed Aβ-induced paralysis and therefore significantly reduced Aβ toxicity. Moreover, sesamin and sesamolin significantly improved Aβ-induced defect in chemotaxis behavior and reversed the defect back to normal. However, we found that only sesamin but not sesamolin extended lifespan in *C. elegans*. These results suggest the potential of sesame lignans as a source for the development of anti-Alzheimer’s drug and it is worth doing further investigation of the relationship of lignans structure and their anti-Aβ toxicity activity.

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**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH R01 AG032611

NIH R01 NS077239

**Title:** Antibodies targeting truncated Asp421 tau protein clear human Alzheimer's tau and prevent its toxicity in primary neuronal and mixed cortical cultures

**Authors:** ***S. R. MODAK**, E. M. SIGURDSSON
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**Abstract:** Cleavage at aspartate in position 421 (Asp421) of the tau protein is a hallmark feature of tau pathology in Alzheimer's disease (AD) and related tauopathies. This truncated form of the protein is postulated to have a role in their pathogenesis by promoting seeding at an early stage, although others suggest that it appears at a later stage. Various tau immunotherapies are currently in clinical trials but this epitope has received limited attention. We previously reported that two Asp421 targeting monoclonal antibodies (mAbs) clear AD derived paired helical filament (PHF)-enriched tau intracellularly when the mAb is added after PHF has been internalized (Modak SR et al, SFN 2015, 579.14). Here, we co-treated primary neurons (PN) or mixed cortical culture (MC) from transgenic tauopathy mice (JNPL3) with these same mAbs or IgG1 control and PHF (both at 10 μg/ml). The purpose of the co-administration was to primarily focus on the benefits of their direct extracellular interaction. Subsequently, western blots were conducted at different time points (24 h, 48 h, 72 h and 96 h) with various markers. Maximal effects of PHF and mAbs were observed at 96 h. The two mAbs, 5G2 and 1G11 have differing affinity for the free Asp421 epitope, $10^{-9}$ vs. $10^{-6}$ M, respectively. PHF was toxic in both culture models based on levels of NeuN, which is a neuronal marker (PN: 49%-, MC: 53% reduction at 96 h), and this toxicity was completely prevented by the higher affinity mAb, 5G2, in both models ($p<0.001$), whereas control IgG1 had no effect. The lower affinity mAb, 1G11 had less pronounced effect in blocking PHF toxicity (PN: 44%-, MC: 24% reduction at 96 h, $p<0.0001$ vs 0.001). For 5G2, this was associated with clearance of total tau (PN: 93%-, MC: 91% reduction at 96 h, compared to PHF+IgG1 control, $p<0.0001$ for both) and phospho-tau (PN: underway, MC: 95% reduction at 96 h, $p<0.0001$). The 1G11 mAb was less effective and cleared total tau only in PN (48% at 96 h, $p<0.0001$) and did not clear phospho-tau in MC (PN analysis is underway). Analysis of Iba1 levels in MC as a marker of microgliosis revealed dramatic increase

in Iba1 over time in PHF treated culture (1083% over untreated cells at 96 h, $p<0.0001$), which was completely prevented by 5G2 ($p<0.0001$) but only slightly by 1G11 (862% over untreated cells, $p<0.0001$). However, the 1G11-mediated reduction in microgliosis was significant compared to the PHF-treated culture (19%, $p<0.0001$). In conclusion, this study clearly illustrates the therapeutic potential of the higher affinity mAb, 5G2, in targeting the pathological Asp421 tau epitope, derived from human AD brain, to prevent its toxicity and associated microgliosis, as well as to enhance tau and phospho-tau clearance.

**Disclosures: S.R. Modak:** None. **E.M. Sigurdsson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EMS is an inventor on patents on tau immunotherapy and related diagnostics that are assigned to New York University and licensed to H. Lundbeck A/S.. F. Consulting Fees (e.g., advisory boards); H. Lundbeck A/S (within the last year), GlaxoSmithKline (within the last year).

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.20/T5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH R01 AG032611

NIH R01 NS077239

Alzheimer's Association 2016-NIRG-397228

Blas Frangione Foundation

**Title:** Partial humanization alters antibody charge and impairs primarily intracellular- but to some extent extracellular efficacy in targeting pathological tau protein

**Authors: *E. E. CONGDON**[1], J. CHUKWU[2], D. UJLA[1], D. B. SHAMIR[1], H. B. R. SAIT[1], X. KONG[3], E. M. SIGURDSSON[4]
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**Abstract:** Maximizing tau antibody (Ab) efficacy may require Abs that target tau both extra- and intracellularly. Previously, we simulated these situations by treating primary neuronal cultures in two ways. PHF tau enriched from Alzheimer’s brain and tau Ab were added either together (PHF+Ab) or Ab 24 h after PHF (PHF→Ab). In the former approach, the tau and Ab primarily interact extracellularly. In the latter approach, Ab uptake is required for efficacy in preventing

PHF-induced toxicity and pathology. Ab uptake into neurons depends on multiple factors including their charge as indicated by their isoelectric point (IEP). In the first set of experiments, we assessed efficacy of three Abs: 1B9 (P-Thr 212/P-Ser214; IEP=8.0); 2C11 (P-Ser262; IEP=7.8) and; Tau-5 (210-244; IEP=5.1), in the dosing methods described. Although the Abs showed efficacy under the extracellular PHF+Ab condition, they were ineffective in the PHF→Ab paradigm. These differences could be explained by their limited neuronal uptake. Confocal imaging and western blots analysis showed that all three had significantly less neuronal uptake than 4E6, an Ab known to be efficacious under both conditions ($p \leq 0.0001$ for all). However, their epitope differences complicate interpretation of their efficacy profile. To address this issue, we compared efficacy of mouse 4E6 (IEP=6.5) and its partially humanized derivative, h4E6 (IEP=9.6), in the two assays. PHF alone induced toxicity (85% increase in LDH and 94% decrease in NeuN, $p \leq 0.05$, 0.001 compared to control), and increased total and phospho-tau (p-tau) levels (6.7-fold and 5.1-fold control) in the remaining neurons. In both the PHF+Ab and PHF→Ab dosing paradigms, unmodified 4E6 prevented this toxicity based on NeuN as well as total and p-tau ($p \leq 0.0001$ for all), and resulted in values comparable to untreated control. The change in 4E6's IEP with humanization was accompanied by a loss of efficacy in the PHF→Ab paradigm (86% loss of NeuN as well as 3.9- and 4-fold increase in total and p-tau in the remaining neurons). In the PHF+Ab paradigm, the h4E6 retained efficacy in preventing increases in tau levels (0.49-fold above and 0.2-fold below untreated control for total and p-tau, $p \leq 0.01$, 0.002) but was not as effective as m4E6 in preventing toxicity (61% NeuN loss compared to 94% for PHF alone; $p \leq 0.01$). These results show that neuronal uptake of tau Abs improves their efficacy. As importantly, because uptake is to a large extent governed by charge, Ab humanization may greatly affect its efficacy, irrespective of its binding to the target. Finally, the humanization may affect extracellular efficacy because of subtle changes to its target binding site.

**Disclosures: E.E. Congdon:** None. **J. Chukwu:** None. **D. Ujla:** None. **D.B. Shamir:** None. **H.B.R. Sait:** None. **X. Kong:** None. **E.M. Sigurdsson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EMS is an inventor on patents on tau immunotherapy and related diagnostics that are assigned to New York University and licensed to H. Lundbeck A/S.. F. Consulting Fees (e.g., advisory boards); H. Lundbeck A/S (within the last year), GlaxoSmithKline (within the last year).

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.21/T6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

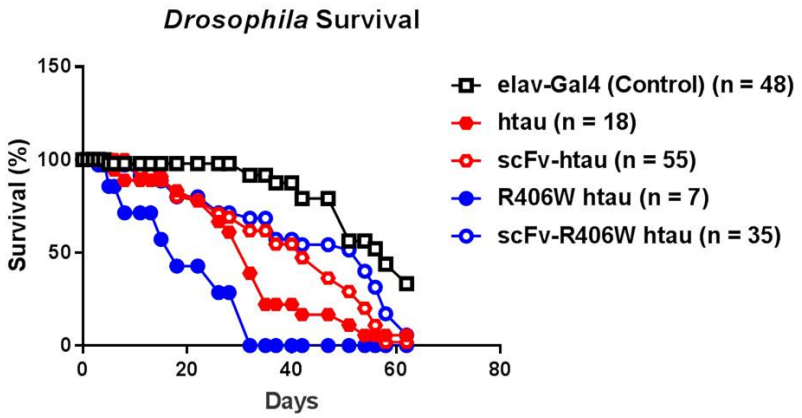
**Support:** NIH Grant R01 AG032611

NIH Grant R01 NS077239

**Title:** Therapeutic potential of an anti-tau single chain variable antibody fragment assessed in *Drosophila* models of tauopathy

**Authors: *S. KRISHNASWAMY**[1], H. D. RYOO[2], E. M. SIGURDSSON[3]
[1]Neurosci. and Physiol., [2]Cell Biol., [3]Neurosci. and Physiology, and Psychiatry, New York Univ. Sch. of Med., New York, NY

**Abstract:** We have identified numerous single chain variable fragments (scFv) of tau antibodies from phage display libraries derived from monoclonal tau antibody hybridomas. We subsequently characterized further one of these scFv and showed its promise as an imaging diagnostic agent to identify tauopathies in live animals (Krishnaswamy S et al, J Neurosci Dec 10, 2014).
Here, we examined its therapeutic potential in two transgenic (tg) *Drosophila* tauopathy models that express wild-type human tau (htau) or the familial human tauopathy mutation R406W. All the flies expressed the transgene specifically in neurons (elav-Gal4 promoter). scFv expressing flies were crossed with the tauopathy flies, the number of hatched flies were counted, and their survival curve determined. Overall, the survival curves were very significantly different (log-rank test, $p<0.0001$). Control flies with the neuronal promoter survived the longest. On the other hand, tg R406W flies had the shortest live span, which was greatly prolonged by co-expressing the anti-tau scFv ($p=0.0004$). Likewise, tg htau flies had a moderately short live span, which was prolonged by co-expressing the anti-tau scFv ($p=0.09$). In addition, the tau transgenes led to developmental toxicity, which was prevented by the scFv, based on the number (n) of hatched progeny that are expressing tau transgenes in comparison with the predicted mendelian ratio of those flies: Control (n=48); tg htau (n=18); scFv-htau (n=55), tg R406W (n=7); scFv-R406W (n=35). We are currently examining various tau fractions in these flies at different time points to clarify the mechanism of this pronounced therapeutic effect.
In summary, these findings support the therapeutic potential of anti-tau scFv and the use of *Drosophila* models for such screening.



**Disclosures:** **S. Krishnaswamy:** None. **H.D. Ryoo:** None. **E.M. Sigurdsson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EMS is an inventor on patents on tau immunotherapy and related diagnostics that are assigned to New York University and licensed to H. Lundbeck A/S.. F. Consulting Fees (e.g., advisory boards); H. Lundbeck A/S (within the last year), GlaxoSmithKline (within the last year).

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.22/T7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA/NIHR01AG051674

**Title:** SCF+G-CSF synergistically increases amyloid beta removal by bone marrow-derived monocytes

**Authors: *L.-R. ZHAO**[1], B. LI[2]
[1]SUNY Upstate Med. Univ., Syracuse, NY; [2]Neurol., LSUHSC-S, Shreveport, LA

**Abstract:** Alzheimer's disease is a rapidly growing health problem worldwide. Impairments in Aβ clearance play a key role in Alzheimer's disease development and progression. Stem cell factor (SCF) and granulocyte-colony stimulating factor (G-CSF), the two essential hematopoietic growth factors, have been demonstrated their synergistic efficacy in hematopoietic stem cell mobilization. Here we have determined the synergistic effectiveness of SCF+G-CSF in Aβ clearance by bone marrow-derived monocytes/macrophages (BMDMMs) through both *in vivo* and *in vitro* approaches. Male APP/PS1 mice (10 month old) were randomized to receive 12- day injections (s.c.) of either vehicle solution, SCF (200μg/kg), G-CSF (50μg/kg), or SCF+G-CSF. Age-matched wild-type (WT) mice served as normal controls. We observed that only SCF+G-CSF-treated APP/PS1 mice showed a long-term and stable recovery in spatial learning and memory that was examined by a water maze 3 and 7 months after treatment. SCF+G-CSF treatment also synergistically reduced the Aβ load in the brain 8 months after treatment. In addition, we also found that the recruitment of BMDMMs ($Iba1^+$ cells) and the association of the BMDMMs with Aβ plaques in the brains of APP/PS1 mice were increased by SCF+G-CSF one day after the final injection. The *in vitro* data further confirmed that SCF+G-CSF synergistically enhanced uptake of aggregated Aβ by BMDMMs in a dose- and time-dependent manner. These findings reveal that the combination of SCF and G-CSF treatment leads to a synergistic and long-term therapeutic effects in cognitive improvement and Aβ clearance in a mouse model of cerebral amyloidosis. Promoting Aβ removal by BMDMMs plays a critical role in SCF+G-CSF-enhanced Aβ clearance. This study provides new insights into the contribution of

hematopoietic growth factors in restricting the progression of Alzheimer's disease. This study was supported by the National Institute On Aging of the National Institutes of Health in the United States (R01AG051674).

**Disclosures: L. Zhao:** None. **B. Li:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.23/T8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** the National Nature Science Fund of China 81271430

Guangdong Provincial Universities fund 2012-328

**Title:** AAV9-mediated Cdk5 inhibitory peptide reverses pathological changes and behavioral deficits in the AD model mice

**Authors: *Y. HU**[1], Y. HE[2], S. PAN[3], M. XU[3], R. HE[3], W. HUANG[3], P. SONG[3], J. HUANG[4], H. ZHANG[5]
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**Abstract:** Cdk5, binding to and activated by p35, phosphorylates multiple substrates and plays an essential role in the development and function of the central neuron system. However, proteolytic production of p25 from p35 under stress conditions leads to inappropriate activation of Cdk5 and contributes to hyperphosphorylation of tau and other substrates related to the pathogenesis of Alzheimer's disease (AD). Selective inhibition of aberrant Cdk5 activity via genetic overexpression of Cdk5 inhibitory peptide (CIP) reduces pathological changes and prevents brain atrophy and memory loss in p25-transgenic mice. In the present study, we delivered AAV9-GFP-CIP into brain cells via intracerebroventricular infusion in APP/PSEN1 double transgenic mice at 3-month-old, after the occurrence of β amyloid (Aβ) aggregation and hyperphosphorylation of tau. Three months treatment of AAV9-GFP-CIP reduced pathological changes including tau hyperphosphorylation, Aβ deposit, astrocytosis and microgliosis, which were correlated with the reversal of memory loss and anxiety-like behavior observed in APP/PS1 mice. Neuroprotection effect of AAV9-GFP-CIP lasted to additional seven months, which was the endpoint of the study. These findings provide a novel strategy to selectively targeting Cdk5 for treatment of AD.

**Key words:** AAV9 · Alzheimer's disease · Cdk5 · Cdk5 inhibitory peptide (CIP) · Tau pathology · β amyloid

**Disclosures:** **Y. Hu:** None. **Y. He:** None. **S. Pan:** None. **M. Xu:** None. **R. He:** None. **W. Huang:** None. **P. Song:** None. **J. Huang:** None. **H. Zhang:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.24/T9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** J. Yang & Family Foundation

DCL is a Paul & Daisy Soros New American Fellow

**Title:** Identifying locomotion kinematics changes reflect Alzheimer's pathological changes using supportive vector machine

**Authors:** ***R. HUANG**[1], H. GHASEMI DAMAVANDI[3], M. S. JOSEPH[2], R. R. ROY[4], H. ZHONG[4], E. H. KOO[6], J. LEITER[7], D. LU[5]
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**Abstract:** Motor function is a means for human and other animals to interact with the surroundings. In the absence of pathology, motor functions are usually coordinated, efficiently, and effortlessly. However, disease or injury can compromise the speed, accuracy, efficiency, and flexibility of motor function execution. This makes it possible that the motor function changes could reflect or even predict the pathological changes. Currently, many motor functions have been listed among the important criteria for diagnosis, such as gait for spinal cord injury rehabilitation evaluation, and reaching and grasping for stroke pathological assessment. However, most of the current motor-function-based diagnosis has three major disadvantages: 1) the overall motor function in healthy subjects or experimental animals is not quantitatively characterized; 2) current motor function analysis methods are not sensitive enough for pre-clinical or progressive changes; 3) the analysis features are usually empirically derived, not suited for diseases that are not well characterized. In this study, we established a mathematical model that automatically tracks locomotion pattern through supportive vector machine in an Alzheimer's disease mouse model (J20). Our results show that our model can select locomotion

kinematic features that accurately (87.10% accuracy) detect and classify the J20 mouse from their wildtype littermates.

**Disclosures: R. Huang:** None. **H. Ghasemi Damavandi:** None. **M.S. Joseph:** None. **R.R. Roy:** None. **H. Zhong:** None. **E.H. Koo:** None. **J. Leiter:** None. **D. Lu:** None.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.25/T10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** ADDF

**Title:** Novel partial mitochondrial complex i inhibitors as disease-modifying therapy for Alzheimer’s disease

**Authors: *S. TRUSHIN**
Neurol., Mayo Clin., Rochester, MN

**Abstract:** Key words: mitochondrial complex I, Alzheimer’s Disease, drug discovery
Alzheimer’s Disease (AD) has no effective treatments, and recent clinical trials focused on prevention of amyloid beta (Aβ) production have consistently failed. Alternative approaches are urgently needed. We recently demonstrated that modulation of mitochondrial function with a small molecule tricyclic pyrone compound CP2 prevents the development of cognitive and behavior phenotypes in multiple transgenic mouse models of familial AD. Target identification conducted using low-mass molecular dynamic simulations, pull-down and competitive binding assays, multiple biochemistry and enzymatic approaches revealed that CP2 competes with the flavin mononucleotide (FMN) for binding to the redox center of mitochondrial complex I (MCI) *partially* reducing its activity (EBioMedicine, 2015, PMID 26086035). Here, we describe new classes of compounds small molecule inhibitors of FMN site of MCI including a novel lead compound NSMC00594 developed using rational design and extensive structure-activity relationship studies. In cellular assays, novel MCI inhibitors protect against Aβ toxicity in MC65 Tet On/Off cellular model of AD, mildly inhibit MCI activity decreasing NAD+/NADH ratio with minimal toxicity in primary mouse embryonic neurons. Binding of the lead compound NSMC00594 to the FMN site of MCI was confirmed using a pulldown and competitive binding assays, and surface plasmon resonance technology. Chronic administration of NSMC00594 to APP/PS1 and non-transgenic mice via drinking water over 8 months did not affect the development in the progeny and had no detectable toxicity or side effects at 2x of therapeutic dose. NSMC00594 has good oral bioavailability and penetrates the blood brain barrier. Pre-symptomatic treatment of APP/PS1 mice with NSMC00594 resulted in cognitive protection after

6 months of chronic oral administration. Mechanistic studies demonstrate that MCI inhibitors induce mitochondrial biogenesis, enhance cellular energetics, induce a protection against oxidative stress and engage other mechanisms that intersect with the pathways involved in longevity and health extension. Our studies present the evidence that modulation of MCI activity by the novel partial MCI inhibitors averts cognitive decline in Alzheimer's Disease representing novel therapeutic approach.

**Disclosures:** **S. Trushin:** A. Employment/Salary (full or part-time):; full.

**Poster**

**478. Preclinical Therapeutic Strategies for Neurodegenerative Disease II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 478.26/T11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIEHS R01ES020715

ADDF 291204

Bright Focus A2011084

Mayo Clinic ADRC

NCATS UL1 TR000135

**Title:** Targeting mitochondrial complex i activity averts cognitive decline in symptomatic animal model of familial Alzheimer's disease

**Authors: *A. STOJAKOVIC**[1], B. GATENO[2], U. TRIPATHI[2], P. FLANNERY[2], S. TRUSHIN[2], J. WILKINS[2], E. TRUSHINA[2]
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**Abstract:** Alzheimer's disease (AD) is the leading cause of dementia with an estimated global prevalence of 24 million individuals. Incidences of this disease are expected to double every 20 years emphasizing an urgent need for a development of disease modifying therapeutic strategies. A substantial body of clinical evidence has framed AD in the context of metabolic dysfunction and its pathophysiological importance to disease progression, suggesting that modulation of cellular energetics could represent new therapeutic approach. In our previous research, we have demonstrated that modulation of mitochondrial complex I activity using a tricyclic pyrone compound CP2 is effective in clearing both amyloid beta (Aβ) and phosphorylated Tau, augmenting mitochondrial bioenergetics, promoting resistance to oxidative stress and restoring mitochondrial transport, levels of BDNF and synaptic proteins in presymptomatic APP/PS1

mice. In parallel, these mice demonstrated an improved cognitive and behavioral phenotype over their untreated littermates.
In our current study, we tested whether CP2 treatment could halt the disease progression in symptomatic APP/PS1 mice. We also evaluated treatment efficacy based on multiple parameters informative of healthy aging in chronologically aged non-transgenic (NTG) littermates. Both APP/PS1 and NTG mice displayed improved cognitive and motor performance following chronic CP2 treatment over 13 months compared to untreated counterparts. CP2-treated mice displayed reduced levels of inflammation and senescent cells, and APP/PS1 mice had reduced levels of soluble Aβ. We defined the molecular mechanism underpinning this improvement by assessing biochemical pathways involved in the mechanisms of longevity, mitochondrial bioenergetics/signaling, neurotransmitter trafficking, and oxidative stress using multiple techniques and systems biology approaches. Our results suggest that modulation of mitochondrial complex I activity with small molecules represents a promising therapeutic approach to ameliorate AD and promote healthy aging.
**Keywords:** Alzheimer disease, aging, symptomatic APP/PS1 mice, drug discovery.

**Disclosures:** **A. Stojakovic:** None. **B. Gateno:** None. **U. Tripathi:** None. **P. Flannery:** None. **S. Trushin:** None. **J. Wilkins:** None. **E. Trushina:** None.

**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.01/T12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Selection of general amyloid interaction motif (GAIM)-Ig-fusions with increased targeting activity for misfolded beta amyloid and tau

**Authors: *E. K. ASP**[1], M. PROSCHITSKY[1], M. LULU[1], C. CHUNG[1], C. ROCKWELL-POSTEL[1], H. TSUBERY[1], J. M. LEVENSON[2], K. MCDOWELL[2], J. WRIGHT[1], R. FISHER[1], R. KRISHNAN[1]
[1]Biochem, [2]Preclinical, Proclara Biosci., Cambridge, MA

**Abstract:** The general amyloid interaction motif (GAIM) derived from the M13 phage tip protein g3p binds a wide variety of amyloids in a conformation-dependent manner. Dimeric GAIM-Ig-fusions robustly bind and remodel Aβ42 amyloid and tau fibers. In transgenic models of AD and tauopathy, GAIM-fusion treatment reduces Aβ plaque load, phospho-tau levels and improves cognition. In this study, we explored the mechanism of GAIM-mediated remodeling of amyloids by mutagenesis. Using this data, we designed next generation Ig-fusions which in addition to showing improved binding potency to multiple amyloid aggregates, have reduced potential for immunogenicity after removal of potential T-cell epitopes.

Data obtained from H/D exchange NMR studies, GAIM-peptide-based inhibition assays and computational modeling was used for targeted mutagenesis of the GAIM scaffold. Stable, high expressing variants were then screened for binding to Aβ42 and Tau-K18 fibers using SPR and binding ELISA assays. High binding variants were further screened for Aβ42 fiber remodeling as well as tau and α-synuclein transmission inhibition activities. An independent mutagenesis program was carried out to sequentially eliminate potential T-cell epitopes of GAIM.
GAIM-Ig-fusions identified in the screen with increased amyloid binding and remodeling activity fall into two main categories: 1) variants with reduced interdomain interaction of N1 and N2 domains of GAIM and 2) alterations of specific residues facing the interdomain groove of N1 and N2 domains. Binding specificity depends on the stability of both domains and the melting temperature for domain separation. Over-stabilizing of N1 or N2 domains leads to reduced binding activity, while destabilizing of the domains leads to increased non-specific binding. The data elucidated a novel mechanism for amyloid binding of GAIM mediated by residues facing the interdomain groove of N1 and N2 domains. We hypothesize progressive binding and rearrangement of GAIM β-strands enables GAIM to bind to and remodel amyloids into non-fibrous and non-pathogenic aggregates.
GAIM-Ig-fusions represent a novel class of therapeutics to treat protein misfolding disorders. This study presents recent discoveries in the structure-activity relationship of GAIM and potential candidates with improved *in vivo* efficacy for reducing the accumulation of amyloid plaque and the spread of intracellular tau tangles.

**Disclosures:** **E.K. Asp:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **M. Proschitsky:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **M. Lulu:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **C. Chung:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **C. Rockwell-Postel:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **H. Tsubery:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **J.M. Levenson:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **K. McDowell:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **J. Wright:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **R. Fisher:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA. **R. Krishnan:** A. Employment/Salary (full or part-time):; Proclara Biosciences, Cambridge, MA.

**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.02/U1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Evaluation of cGMP in CSF sampled from the cisterna magna as a biomarker for centratl PDE2 inhibition in the dog

**Authors: *H. BORGHYS**[1], D. DHUYVETTER[2], P. BUIJNSTERS[2], L. VER DONCK[2], R. VREEKEN[2]
[1]Janssen Res. & Develop., Beerse, Belgium; [2]Janssen Res. @ Develop., Beerse, Belgium

**Abstract:** PDE2A, which plays a role in the regulation of intraneural cGMP and CMP in the brain, is mainly expressed in the areas involved in emotion, perception, concentration, learning and memory. It is assumed to play an important role in CNS disorders such as depression and anxiety. PDE2A inhibitors are being investigated for treatment of cognitive impairment in Alzheimer's disease. We have developed a preclinical model in dogs to evaluate the activity of PDE2A inhibitors in the brain. A needle guide is placed in the skull of the dogs to sample CSF directly from the lateral ventricle in conscious animals. cGMP in CSF is used as a biomarker for functional activity following PDE2A inhibition. Repeated sampling enables the longitudinal follow up of cGMP in the CSF. Clear dose related increases in cGMP are seen after administration of PDE2A inhibitors. This model enables the ranking of compounds preclinically for in vivo activity, setting of safety margins and human dose prediction. Since it is not possible to sample the lateral ventricle in humans and to address the potential use of cGMP in CSF as a biomarker in clinical trials, we evaluated the effect of a PDE2A inhibitor on cGMP in CSF sampled more downstream. The cisterna magna was chosen as sampling site since lumbar CSF sampling in dogs is more difficult compared to humans. We found that cGMP concentrations in CSF sampled from the cisterna magna were much lower than in the lateral ventricle. Compared to the dog own baseline values, a dose related increase in cGMP was seen after dosing a PDE2A inhibitor. However, increases in cGMP in CSF compared to baseline were also seen in some vehicle dosed dogs. A more extensive longitudinal follow up of untreated and vehicle dosed dogs is required to have an idea on the fluctuations of cGMP in the cisterna magna and address the potential value of cGMP as a biomarker for PDE2A inhibition in the brain in humans.

**Disclosures: H. Borghys:** A. Employment/Salary (full or part-time):; Janssen. **D. Dhuyvetter:** A. Employment/Salary (full or part-time):; Janssen. **P. Buijnsters:** A. Employment/Salary (full or part-time):; Janssen. **L. Ver Donck:** A. Employment/Salary (full or part-time):; janssen. **R. Vreeken:** A. Employment/Salary (full or part-time):; Janssen.

**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.03/U2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Internal Medicine Departmental Funds

**Title:** Adipose tissue-targeted stem cell therapy for Type 2 Diabetes-related CNS dysfunction

**Authors: *S. SAIEVA**[1,4], H. S. SALLAM[1], B. KRISHNAN[2,3], B. TUMURBAATAR[1], G. LA ROCCA[4], R. ANZALONE[4], G. TAGLIALATELA[2,3], N. ABATE[1]
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**Abstract:** Compelling evidence indicates that Type 2 Diabetes (T2D) and Alzheimer's Disease (AD) may possibly share a common pathological origin, but the underlying mechanisms remain poorly understood. T2D is a known risk factor for AD, while insulin resistance (hallmark of T2D) has been extensively documented in AD patients and insulin has an important role in learning and memory.We developed a mouse model (AtENPP1Tg mouse) that recapitulates typical characteristics of human metabolic syndrome and insulin resistance, which presents also brain dysfunction, specifically in hippocampus, thus offering a unique chance to explore which mechanistic pathways connect diabetes with AD.Interestingly, the pool of mesenchymal stem cells (MSCs) in many organs, included adipose tissue, of diabetic patients, is significantly reduced, as well as their role in regeneration is dramatically reduced. We hypothesize the existence of an axis between adipose tissue and CNS, in which adipose tissue-residing-MSCs deliver messages to CNS. When adipose tissue becomes insulin resistant, the amount of MSCs reduces, hence the adipose tissue-brain axis is impaired resulting in both peripheral and brain insulin resistance.Therefore, in order to investigate this relationship, we injected via subcutaneous route, human umbilical cord-derived Wharton's Jelly (WJ) mesenchymal stem cells (MSCs), directly into the adipose tissue, thus reestablishing the cross-talking between peripheral organs and brain. First, we evaluated blood glucose levels in transgenic transplanted mice compared to not -transplanted; then, we assessed the LTP response in hippocampus between the two groups; finally, we investigated if insulin signaling was restored in synaptosomes isolated from both transplanted and not-transplanted mice.It is conceivable that these beneficial effects are mediated by MSC-derived exosomes, delivered to CNS from the periphery, therefore the replenishment of MSCs may restore insulin signaling both in periphery and CNS, thus reestablishing adipose tissue-brain cross-talking.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.04/U3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH grant MH102065 to JDG

NIH grant 1 K76AG054772 to ACP

BrightFocus Foundation grant to ACP

**Title:** Glutamatergic modulation rescues behavior in an amyloid mouse model of Alzheimer's disease

**Authors: C. LARSON**[1], R. DAVIDSON[2], M. OKAMOTO[2], B. S. MCEWEN[3], J. D. GRAY[4], *A. C. PEREIRA[5]
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**Abstract:** Alzheimer's disease (AD) is the most common neurodegenerative disorder characterized by progressive impairment of memory and cognition. At the cellular level, AD patients exhibit cerebral accumulation of extracellular amyloid plaques, composed of amyloid-beta and intraneuronal neurofibrillary tangles, formed of phosphorylated tau. It has become an international public health epidemic with an enormous psychological and economical impact in society with an urgent need for novel treatments. Previous data suggest that release of amyloid-beta and tau is dependent on neuronal activity. Furthermore, oligomers of amyloid-beta disrupt glutamate transporter, leading to spill over to extrasynaptic space, local activation of NMDA receptors and inhibition of long-term potentiation. We hypothesized that modulation of glutamatergic systems, via enhancement of the major glutamate transporter EAAT2, could be beneficial in an Alzheimer's disease mouse model (5xFAD). The 5xFAD mice carry 3 of the autosomal dominant human APP mutations and 2 of the presenilin mutations and develop amyloid plaques. In this study, Riluzole, a glutamate modulator that has been shown to increase EAAT2 expression, was used to treat 5xFAD mice from 1 to 6 months of age. Memory performance was then tested in the Y-maze test, a spatial memory task dependent on the hippocampus. 5xFAD mice treated with riluzole showed prevention in spatial memory decline in comparison to 5xFAD mice treated with water and performed at the same level as age-matched wild-type mice. We are currently performing biochemical and RNA-sequencing analysis in these samples to investigate the underlying molecular mechanisms of the behavioral rescue in this amyloid mouse model and evaluating if it is also associated to genes related to neuroplasticity and neural communication as we have published in an aging model before.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.05/U4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Discovery of novel brain permeable and g-protein biased beta1-adrenergic receptor partial agonists for the treatment of neurocognitive disorders

**Authors: *B. YI**[1,2], A. JAHANGIR[2], A. K. EVANS[2], D. BRIGGS[2], K. RAVINA[2], J. ERNEST[2], A. B. FARIMANI[3], W. SUN[4], J. RAJADAS[4], M. J. GREEN[2], E. N. FEINBERG[3], V. S. PANDE[3], M. SHAMLOO[2]
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**Abstract:** The beta1-adrenergic receptor (ADRB1) is a promising therapeutic target involved in the cognitive deficits and pathological features associated with Alzheimer's disease (AD). Evidence indicates that ADRB1 plays an important role in regulating neuroinflammatory processes, and activation of ADRB1 may produce neuroprotective effects in neuroinflammatory diseases. Novel small molecule modulators of ADRB1, engineered to be highly brain permeable and functionally selective for the G-protein with partial agonistic activity, could have tremendous value both as pharmacological tools and potential lead molecules for further preclinical development.
Xamoterol is a highly selective partial agonist of ADRB1. However, its therapeutic utility as a CNS drug is limited due to its poor oral bioavailability and brain penetration. As part of our program to discover functionally selective partial agonists of ADRB1 that have potential therapeutic value for AD and neuroinflammatory disorders, we have explored the structure-activity relationship of xamoterol derivatives. Our medicinal chemistry effort led to the discovery of a series of compounds. As functionally selective agonists of ADRB1, these compounds produce partial agonistic activity on G-protein signaling with $EC_{50}$ values in the low nanomolar range, but engage very little beta-arrestin recruitment compared to the unbiased agonist isoproterenol. The compounds also inhibit the tumor necrosis factor α (TNFα) response induced by lipopolysaccharide (LPS) both *in vitro* and *in vivo*, and show high brain penetration. The newly identified, functionally selective partial agonists of ADRB1 are invaluable research tools to study mechanisms of G-protein coupled receptor signal transduction.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.06/U5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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

**Title:** Cannabinoid-based alzheimer therapy: Effects of tetrahydrocannabinol on anxiety, memory and neuron loss in Tg4-42 mice

**Authors: *Y. BOUTER**[1], M. E. SICHLER[1], M. J. LOEW[1], P. TUCHOLLA[1], C. BOUTER[2], T. A. BAYER[1]
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**Abstract: Introduction:** Limited therapeutic effects of current Alzheimer (AD) treatments highlight the need for new research approaches. Drugs that simultaneously target different aspects of AD could provide therapeutic benefits. Targeting the endocannabinoid system could be such an approach. Endocannabinoid signaling has been demonstrated to be involved in memory formation, motor control, inflammation & oxidative stress. Several *in vitro* studies showed that cannabinoids reduce Aβ-induced neurotoxicity as well as cell death & facilitate neurogenesis. Recently, it could be demonstrated that cannabinoids stimulate the removal of intraneuronal Aβ *in vitro*. The aim of the study was to investigate the multi-faceted therapeutic potential of Tetrahydrocannabinol (THC). For the first time the neuroprotective properties of THC were studied *in vivo using* Tg4-42 mice. These mice expressing Abeta4-42 develop severe hippocampal neuron loss & memory deficits.
**Material & Methods:** Five months old male & female Tg4-42 Alzheimer mice were treated daily with Tetrahydrocannabinol (20mg/kg) for six weeks. Sex and age-matched control Tg4-42 mice treated with the Vehicle solution (5% ethanol, 5% Tween80 in 0,9% sodium chloride solution) were used a control group. Behavior tests were performed assessing memory, motor functions & anxiety (Rotarod, Novel Object Recognition, Elevated-Plus-Maze, Dark/Light & Water Maze). Design-based Stereology will be used to analyze neuron loss in Tg4-42.
**Results & Discussion:** THC-treatment ameliorates motor performance in Tg4-42. Treated mice showed a significantly better performance on the Rota Rod compared to control mice. Recognition memory in the novel object recognition task was improved in THC-treated Tg4-42. Furthermore, THC-treatment caused alterations in the anxiety behavior. In addition, the effects of THC on spatial reference memory will be presented as well as the effects on neuron loss in the CA1 region of the hippocampus. In conclusion, the present study shows that chronic THC

treatment can be therapeutic beneficial for several altered parameters in AD including motor deficits, anxiety & memory. Our findings reinforce a cannabis-based medicine as a potential therapy against AD.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.07/U6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** The Konsul Thure Carlssons Minne Foundation

The Swedish Research Council

The Thorsten and Elsa Segerfalk Foundation

**Title:** Voluntary exercise increases ganglion cell survival in retinas of 5xFAD mice

**Authors: *O. MANOUCHEHRIAN**[1,2], M. SVENSSON[3], T. DEIERBORG[3], L. TAYLOR[2]
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**Abstract:** Retinal ganglion cell (RGC) loss is a feature of the early stages of Alzheimer's disease (AD), although the mechanism behind this phenomenon has yet to be fully elucidated. Recent studies of experimental AD models suggest that amyloid precursor protein and amyloid-beta (Aβ) deposition may contribute to RGC degeneration. The Aβ load in the brain of familial Alzheimer's disease (FAD) mice has been found to be ameliorated with voluntary exercise. Here, we investigate if the effect of voluntary exercise extends to ganglion cell survival and retinal Aβ load in 5xFAD mice.
From 2 months of age, 5xFAD mice were voluntarily exercised for 6 months (n = 12) or kept sedentary (n = 14) and compared to age-matched wildtype controls (n = 6).
Immunohistochemistry was used to quantify Aβ deposition (Aβ), ganglion cell survival (NeuN and RBPMS) and glial reactivity (Iba1 and GFAP).
We found that both 5xFAD groups displayed significantly elevated Aβ load in the ganglion cell layer, and fewer RGC's compared to wildtype controls. However, exercised 5xFAD mice displayed a significantly increased RGC survival ($p>0.0001$) compared to sedentary 5xFAD counterparts, despite no significant difference in Aβ load. The RGC rescue effect of exercise was on average 45% (95% CI = 28%, 62%) using RBPMS and 24% (95% CI = 13%, 34%) using NeuN. No significant differences with regards to glial reactivity (GFAP and Iba1) were observed

between any of the three groups.
In support of previous studies showing potential positive role of exercise in AD, as well as visual abnormalities in AD patients and animals, we found a substantial loss of RGCs in 5xFAD mice, which was significantly reduced through voluntary exercise.

**Disclosures: O. Manouchehrian:** None. **M. Svensson:** None. **T. Deierborg:** None. **L. Taylor:** None.

**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.08/U7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Determination of sigma-2 receptor densities in rat cortical neurons, astrocytes and microglia

**Authors: *C. ZENG**, C. WENG, B. P. LIEBERMAN, J. L. MIKITSH, T. A. METZ, R. H. MACH
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**Abstract:** Sigma-2 ligands have been shown to displace beta amyloid (Aβ) oligomer binding to synaptic puncta, prevent and reverse Aβ oligomer-induced synapse loss in primary neuronal cultures, and reverse memory loss in transgenic mouse models of Alzheimer's disease (AD). In order to understand the mechanism of sigma-2 ligands as potential therapeutics, it is necessary to determine the sigma-2 receptor density in different brain cell types. In the current study, primary rat cortical neurons, astrocytes and microglia were cultured and harvested. Sigma-2 receptor densities were determined by receptor binding assay using [$^{125}$I]RHM-4 and [$^{3}$H]DTG. By using [$^{3}$H]DTG our results show that sigma-2 densities in neurons, astrocytes and microglia are 2311 ± 291.5, 2366 ± 185.1, 2835 ± 244.9 (fmol/mg), respectively. Kd values are 82.66 ± 20.58, 52.01 ± 0.90, 43.40 ± 9.04 (nM), respectively. By using [$^{125}$I]RHM-4, our data show that sigma-2 densities in neurons, astrocytes and microglia are 1596 ± 45.6, 1766 ± 40.4, 1637 ± 16.5 (fmol/mg), respectively. Kd values are 1.20 ± 0.10, 0.84 ± 0.06, 0.99 ± 0.03 (nM), respectively. Cell uptake studies of [$^{125}$I]RHM-4 in neurons and astrocytes were also performed. The data show that cell uptake percentages of [$^{125}$I]RHM-4 input are comparable in neurons and astrocytes. These data show that sigma-2 receptors are expressed in rat cortical neurons, astrocytes, and microglia at similar levels, and the binding activities of sigma-2 ligands to neurons and astrocytes are similar. These results imply that sigma-2 ligands reverse Aβ oligomer-induced memory loss possibly by acting upon multiple brain cell types.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.09/U8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** ANR-12-MALZ-0002-01

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University of Strasbourg

CNRS

JNCASR

Department of Biotechnology and the Government of India (Grant/ DBT/ CSH/ GIA/ 1752)

**Title:** Epigenetic correction of defective plasticity in a tauopathy mouse model with an acetyltransferase activator molecule

**Authors: *A.-L. BOUTILLIER**[1], S. CHATTERJEE[1], R. CASSEL[1], A. SCHNEIDER-ANTHONY[1], K. MERIENNE[1], B. COSQUER[1], S. HALDER SINHA[2], M. KUMAR[2], P. CHATURBEDY[3], M. ESWARAMOORTHY[3], S. LEGRAS[4], C. KEIME[4], P. DUTAR[5], P. PETSOPHONSAKUL[6], C. RAMPON[6], J.-C. CASSEL[1], L. BUEE[7], D. BLUM[7], T. K. KUNDU[2]
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**Abstract:** Alzheimer’s disease (AD) is characterized by a progressive loss of plasticity and memory functions, further leading to neuronal loss and dementia. Epigenetic changes, including histone acetylation, have emerged as important contributors of AD pathophysiology. In the adult brain, histone acetylation is associated with activity-regulated transcriptional changes required for synaptic plasticity and memory. In an attempt to re-establish a proper acetylation chromatin landscape and transcriptional programs, a series of studies has tested HDAC inhibition as

therapeutic option and found a protective effect of several HDAC inhibitors in different AD mouse models. As an alternative to HDAC inhibitors, targeting CBP/p300 acetyltransferases that play important roles in neuronal plasticity and cognition has been proposed as new therapeutic strategy in memory associated disorders. We have produced the first permeant HAT activator molecule targeting the CBP/p300 proteins, CSP-TTK21, that acetylates nuclear chromatin in mice brain and improves spatial memory (Chatterjee et al., J Neurosci., 2013; Patent: WO2013160885A1). Here, we demonstrate that deficient synaptic plasticity (dendritic spine formation, LTD) and long term spatial memory can be restored by a treatment with CSP-TTK21 in an AD-like Tau pathology mouse model (THY-Tau22 mice). Using genome wide screenings (ChIP-seq), we showed that CSP-TTK21 restores the down-regulated H2B acetylome in the hippocampus of THY-Tau22 mice, especially at super-enhancer -regulated genes (enriched in H3K27ac). Upon learning, CSP-TTK21 re-established part of the learning-induced hippocampal transcriptome, consisting in the induction of immediate early genes (egr-1, cFos, Arc...) and the down-regulation of neuronal identity genes bearing the H3K27ac/H2Bac signature. This study is the first to provide *in vivo* proof-of-concept evidence that direct activation of CBP/p300 HAT with CSP-TTK21 efficiently and selectively reverses epigenetic, transcriptional, synaptic plasticity, and behavioral deficits associated to AD lesions. We think that our study opens up a new therapeutic avenue to the development of drugs that modulate the epigenome with HAT activators, as a potent alternative to HDAC inhibitors. Restoring neural circuits for the treatment of Alzheimer's disease is a major challenge and the possibility to reinstate some plasticity at a late stage in the diseased brain of AD patients may delay the patient’s decline and improve the patient’s condition and dependency.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.10/U9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG023084

NIH Grant NS034467

Cure Alzheimer's Fund

**Title:** An FDA-approved drug as a therapeutic agent to upregulate PICALM

**Authors: *S. A. BAZZI**, K. KISLER, A. R. NELSON, A. P. SAGARE, Z. ZHAO, B. V. ZLOKOVIC
Biophysics and Physiology, Zilkha Neurogenetic Inst., USC, Los Angeles, CA

**Abstract:** Picalm, phosphatidylinositol binding clathrin assembly protein, is a known genetic risk factor in Alzheimer's disease (AD). In healthy mice and humans, Picalm is highly expressed in brain endothelial cells, is involved in clathrin-mediated endocytosis and trafficking, and clearance of amyloid from the brain across the blood-brain barrier. However, in AD Picalm brain endothelial levels are reduced. Using a Picalm deficient mouse model, we have previously shown that Picalm reduction leads to reduced amyloid clearance from brain and exacerbation of amyloid pathology, which could be reversed by increasing Picalm endothelial expression. Thus, therapeutic strategies that upregulate Picalm expression in the vasculature could lead to novel advancements in AD treatment. Currently, no therapeutic treatment targeting Picalm regulation in AD exists, and existing treatments to ameliorate or slow the progression of AD have met with little or no success. To identify a possible Picalm therapeutic treatment, we developed a luciferase reporter assay and screened a library of 2000 FDA-approved drugs. Secondary screening of the identified hits yielded a compound capable of elevating Picalm mRNA and protein levels in vitro by 1.5-3 fold in a human endothelial cell line. Similarly, the compound increased Picalm protein levels in vivo in the brain endothelium of a Picalm-deficient mouse model compared to vehicle treated littermates. In addition to Picalm upregulation, we found this compound also upregulates low density lipoprotein receptor related protein 1 (LRP1), a key protein involved in clearance of amyloid from brain, but does not affect key elements of the clathrin-mediated endocytosis machinery. Together this data indicates that Picalm upregulation could be a promising new therapeutic technique for AD.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.11/U10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R03 AR063326

**Title:** The mitochondria-targeted antioxidant MitoQ improves memory retention, neuropathology and alters the lipidomic profile of aged 3xTgAD mice

**Authors: *M. L. YOUNG**, S. PATI, B. S. CUMMINGS, J. L. FRANKLIN
Univ. of Georgia, Athens, GA

**Abstract:** Considerable evidence suggests that pathologies occurring before the appearance of amyloid plaques and tangles may have a role in Alzheimer's disease (AD) progression. As oxidative stress is an early occurrence in neurodegeneration, we focus on this pathology as a potential mediator of AD pathology. Dysfunctional mitochondria are a likely a source of reactive species that contribute to increased stress. To further understand mitochondria-mediated oxidative stress, we took advantage of a novel mitochondria-targeted antioxidant mitoquinone mesylate (MitoQ). We previously published data showing that MitoQ treatment of young 3xTg-AD mice prior to pathology development prevents oxidative stress, memory loss and several other AD-like pathologies present in this animal model. To answer the question of whether this same antioxidant treatment would be effective during a later stage in disease progression, we began treatment of mice at 12 months of age. Mice were supplied MitoQ (100 μM) continuously in drinking water for 5 months. Following treatment, mice underwent behavioral assessment and brain tissue was harvested for biochemical assays. Morris Water Maze training, a measure of spatial memory retention, showed that mice treated with MitoQ learned spatial cues an average of 3 days before littermate controls. Additionally, mice treated with MitoQ retained spatial memory better than littermate controls in both short and long-term memory retention task. Sensorimotor deficiencies and escape motivation from the water maze were evaluated and did not prove to be significantly different between treatment groups. In support of our behavioral data, MitoQ also altered several AD-like pathologies in this animal model. Synaptophysin, a marker for synapse loss, was significantly increased in MitoQ treated animals compared to littermate controls. In contrast, indicators of oxidative stress and neurodegeneration, such as nitrotyrosine and astrogliosis were significantly reduced. Additionally, caspase-3 activity and subsequent tau pathology were also both significantly reduced with treatment. Lipidomic studies revealed that MitoQ treatment caused significant changes in oxidation and fatty acid alterations in the blood and elevated levels of stearic acid in hippocampal tissue. Our studies support evidence that mitochondrial dysfunction and the subsequent oxidative stress are key mediators in AD progression and also highlight the potential of mitochondria-targeted antioxidants for AD therapeutics.

**Disclosures: M.L. Young:** None. **S. Pati:** None. **B.S. Cummings:** None. **J.L. Franklin:** None.

**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.12/U11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Arginine-rich beta-sheet breaker peptides as potential tau protein aggregation inhibitors

**Authors: *K. RALHAN**, V. GURU KRISHNAKUMAR, S. GUPTA
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**Abstract:** Microtubule Associated Protein (MAP) Tau is a neuronal protein responsible for stabilizing the axonal microtubules. However, in Alzheimer's disease, tau undergoes several post-translational modifications (PTMs) and self-assembles to form insoluble intercellular aggregates. *In vitro* aggregation of the tau protein can be halted by using inhibitors from various classes of molecules including small molecules, peptide-based fragments, and peptidomimetics. As the in-vitro aggregation of full-length tau occurs over 4-6 days, time taken for an inhibitor assay will be on the order of few weeks thus considerably delaying the initial screening. In the present study, we have used Ac-VQIVYK (PHF6) a tau-derived hexapeptide which is the most aggregation-prone fragment of tau protein as a proxy to screen inhibitors for full-length tau protein. Using experimental and computational approaches, we have rationally designed an Arginine-rich amyloid inhibiting/remodelling peptide-based fragment which can tackle PHF6 aggregation. Short peptides have not found much traction as inhibitors of protein aggregation owing to poor cell internalisation resulting in low potency. To overcome this problem, previously researchers have traditionally grafted or appended the peptide fragments in a stable cell permeable scaffold. In our hybrid peptide design, we have grafted the inhibitor peptide to Arg ($R_n$) stretch which has the property of breaking beta sheets. Arginine is a known kosmotropic which can destabilise proteins. Also, arginine-rich peptides have the advantage of acting as a signal peptide for cell internalisation. Since tau aggregation happens intracellularly, it is important for an inhibitor to internalise into the cell. Thioflavin T (ThT) based aggregation inhibition assay using PHF6 as the substrate revealed that a critical length of Arg stretch is required for the inhibitory peptide to act as a beta-sheet breaker. In combination with fluorescence microscopy and ThT assay, we show that $R_6$ and $R_8$ peptides can inhibit PHF6 aggregation. Furthermore, we wanted to check the ability of the $R_6$ peptide to disassemble preformed PHF6 fibrils. Using molecular dynamics simulations, we show that $R_6$ hybrid peptide can bring morphological changes to the PHF6 fibrils which result in loosely packed beta sheets in comparison to control simulations. These results are useful not only in identifying a potential tau aggregation inhibitor but also in devising a targeted design strategy for modifying aggregation of other amyloidogenic proteins.

**Disclosures: K. Ralhan:** None. **V. Guru KrishnaKumar:** None. **S. Gupta:** None.

**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.13/U12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** A tropomyosin receptor kinase A agonist targeted to the brain using MRI-guided focused ultrasound improves cholinergic activity in a mouse model of Alzheimer's disease

**Authors: *K. XHIMA**[1], H. SARAGOVI[3], K. HYNYNEN[4], I. AUBERT[2]
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**Abstract:** Among the neuronal populations that degenerate in Alzheimer's disease (AD), cholinergic loss most closely correlates with declines in synaptic number and cognitive function. Nerve growth factor (NGF) has been shown to promote neuronal survival and synaptic plasticity of cholinergic neurons, and thereby represents a promising therapy for AD. However, therapeutic efficacy of NGF is limited by its inability to cross the blood-brain barrier (BBB), its short half-life, and adverse effects triggered by NGF activation of p75 receptor in the absence of tropomyosin receptor kinase A (TrkA). Here, we use MRI-guided focused ultrasound (MRIgFUS) for non-invasive, transient and localized BBB opening, to facilitate delivery of a high affinity TrkA-specific ligand in targeted regions. We aim to promote cholinergic function by targeted delivery of a TrkA agonist using MRIgFUS. We used a transgenic (Tg) mouse model of AD with deficits related to cholinergic transmission. Briefly, Tg mice and non-Tg littermates were injected intravenously with a TrkA agonist and MRIgFUS applied to brain regions where TrkA is expressed. Expression of TrkA signaling and key downstream effectors were quantified for mRNA, protein and phosphorylation. We observed an increase in TrkA phosphorylation and downstream signaling activation after treatment. Expression of cholinergic markers were also detected and compared after treatment. These results demonstrate the therapeutic efficacy of a TrkA-specific agonist combined with MRIgFUS delivery in a mouse model of AD.

**Disclosures: K. Xhima:** None. **H. Saragovi:** None. **K. Hynynen:** None. **I. Aubert:** None.

**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.14/V1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG048935

**Title:** Effects of varying voluntary aerobic exercise levels on behavior and neuropathology in aged Tg2576 mice

**Authors: N. FRANCIS**, D. L. POPESCU, M. P. MICHAELOS, L. S. ROBISON, S. SUBZWARI, S. I. BEIGELMAN, S. M. FITZGERALD, J. ARENA, S. A. AMREIN, A. E. KUZMINA, D. A. LITUMA, J. HATFIELD, R. KIM, J. K. SULLIVAN, F. XU, J. DAVIS, B. J. ANDERSON, *J. K. ROBINSON, W. E. VAN NOSTRAND
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**Abstract:** Alzheimer's disease (AD) is a progressively debilitating neurodegenerative disorder affecting nearly 50 million individuals worldwide. Epidemiological and clinical studies have pointed to positive benefits of various lifestyle factors in lowering the risk of cognitive impairments and pathological changes in the brain seen in AD. One such lifestyle factor, cardiovascular exercise, has particularly demonstrated its ability to mitigate cognitive and behavioral impairments and reduce AD pathology in both human and animal studies. Information is lacking, however, in regards to the daily amount, timing of onset, and duration of exercise that produces optimal effects. Here, utilizing the Tg2576 mouse, a model of parenchymal amyloid pathology and cognitive impairment, we sought to understand the effects of different amounts of cardiovascular exercise intervention, through daily access to a running wheel, on more advanced stage disease. This study is the first to determine the benefits of different doses [0h, 1h, 3h, and 12h running wheel access] of long-term exercise intervention from 14 to 18 months of age in Tg2576 mice and in age-matched wild-type (WT) mice. The 1h and 3h running groups exhibited higher intensity patterns of running compared to the 12h groups. Behavioral analyses include Barnes maze, Y maze for spontaneous alternation, novel object recognition, radial arm maze, open field, light/dark box, marble burying/digging, Crawley's three chamber paradigm for social interaction, rotarod, and wire hang. Baseline impairments were found in the Tg2576 mice compared to wild type mice, and preliminary analyses revealed diverse patterns of effects of different doses of exercise in Tg2576 mice versus the WT mice. Analysis of exercise effects on measures of AD pathology, immune response and physiology will also be presented.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.15/V2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Canadian Research Chair Program

The Weston Foundation

**Title:** Chronic deep brain stimulation in an Alzheimer's disease mouse model enhances memory and reduces pathological hallmarks

**Authors: *E. GONDARD**[1], A. MANN[1], D. TAMPELLINI[2], J. A. T. MILSTED[1], D. MARILLAC[1], C. HAMANI[3,4], S. K. KALIA[1,3], A. M. LOZANO[1,3]
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**Abstract:** Alzheimer’s disease (AD) is a progressive degenerative disorder that currently remains extremely disabling. Recent work has shown that deep brain stimulation (DBS) has promising effects in AD patients. In parallel to the clinical trials, we investigated the impact of chronic DBS in 3xTg mice, a well-established animal model of AD. AD mice were assigned to control (Cont), non-stimulation (NS) and stimulation (DBS) groups, along with age matched wild type controls (WT-Cont). Bilateral electrodes were implanted in the entorhinal cortex to deliver chronic high frequency stimulation for 25 days. Animals were tested in memory behavioral tasks, with post-mortem measurements of AD pathological markers. We found that chronic DBS in AD mice normalized their impaired performance in the Morris water maze task to that of the WT group in the 1-hour probe test. In the novel object and novel place preference tasks, AD-DBS mice spent more time at the novel object and novice location compared to AD-NS mice. These cognitive improvements in AD-DBS mice were associated with DBS induced increased neurogenesis in the dentate gyrus, a significant reduction in β-amyloid plaques, a reduction in CA-1 cellular Aβ42 levels, decreased cortical total-tau and *p*-tau, along with decreased hippocampal total-tau. Overall, we show that chronic DBS of the entorhinal cortex in AD mice improves both memory and AD specific pathological markers. These results support further testing of DBS as a potential treatment in AD patients.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.16/V3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** VIEP-BUAP 2016-2017

**Title:** The recombinant C-terminal fragment of the tetanus toxin prevents astrocytosis and protects cholinergic markers in rats with the amyloid-β 25-35 peptide

**Authors: *A. PATRICIO**[1], I. MARTÍNEZ-GARCÍA[2], G. D. APÓSTOL DEL R[1], V. ALEMÁN-ALEMÁN[3], J. AGUILERA[4], I. D. LIMÓN[1]
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**Abstract:** The recombinant C-terminal fragment of the tetanus toxin (Hc-TeTx) is a nontoxic peptide of the tetanus toxin that has been shown to exert neuroprotection in excitotoxic models *in vitro* and *in vivo*. The $A\beta_{25-35}$ peptide induce cholinotoxic effects on the *magnocellular nucleus* (NBM), in addition to produced deterioration of the learning and spatial memory processes. The aim of this work was to evaluate the neuroprotective effect of the Hc-TeTx fragment on astrocytosis and cholinergic markers in rats injured with the $A\beta_{25-35}$ peptide into NBM. Male Wistar rats were used and five experimental groups were formed: 1) intact, 2) $A\beta_{35-25}$ [2μg / 2μL], 3) Hc-TeTx [2μM / 2μL], 4) $A\beta_{25-35}$ [2μg / 2μL] and 5) Hc-TeTx + $A\beta_{25-35}$. Each treatments were administered bilaterally by stereotactic surgery into NBM (AP: -0.6, L: ± 2.7, P: -6.5). Thirty two days post-lesion were euthanasia performed on animals to extract the brains and evaluate astrocytosis (immunohistochemistry for GFAP protein), vesicular acetylcholine transporter expression (VAChT) (western blot) and acetylcholinesterase activity (AChE) (Ellman´s method) in the NBM, the frontal cortex (FCx) and the temporal cortex (TCx). The results show that administration of the $A\beta_{25-35}$ peptide increases the expression of GFAP in NBM (87 %), FCx (154 %) and TCx (89 %) respect to the intact group. However, the Hc-TeTx + $A\beta_{25-35}$ group decreases the number of GFAP-immunoreactive cells in NBM (60%), FCx (97%) and TCx (80%) respect to the $A\beta_{25-35}$ group. Nevertheless, when evaluating VAChT expression in each experimental group, the $A\beta_{25-35}$ group showed a decrease in VAChT expression in the NBM (42 %), FCx (68 %) and TCx (50 %) respect to the intact group. On the other hand, the Hc-TeTx + $A\beta_{25-35}$ group increases the expression of the VAChT in the NBM (35%), the FCx (70%) and the TCx (31%) respect to the group $A\beta_{25-35}$. Finally, when evaluating AChE activity, the $A\beta_{25-35}$ group was found to decrease the AChE activity in the FCx (34%) and TCx (44%) in relation to the $A\beta_{35-25}$ group. When the Hc-TeTx + $A\beta_{25-35}$ group was evaluated, was observed a re-establishment of AChE activity in the FCx (43%) and TCx (26%) respect to the $A\beta_{25-35}$ group. These findings suggest that the Hc-TeTx fragment regulate the astrocytes number and improves long-term cholinergic communication in rats injured with the $A\beta_{25-35}$ peptide.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.17/V4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Sentience Foundation

Drew University

**Title:** The protein kinase C-epsilon (PKC-ε) activator 8-[2-(2-pentylcyclopropylmethyl)-cyclopropyl]-octanoic acid (DCP-LA) improves learning and memory, synaptic density and hippocampal neuronal health in a ferrous-amyloid-buthionine (FAB) rat model of Alzheimer's disease

**Authors: R. F. CANDIA**[1], R. B. KNOWLES[2], *C. R. MCKITTRICK[2]
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**Abstract:** Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive memory loss and hippocampal neurodegeneration. It is estimated to affect nearly 47 million people worldwide, and its prevalence is expected to triple within 35 years. Within the last decade, 99.6% of drugs targeting this disease have failed in clinical trials, and those few that have succeeded have mild effects, at best. Recently, protein kinase C-epsilon (PKC-ε), a serine/threonine kinase, has become a target for drug development for AD. This kinase has been shown to play a role in critical processes related to AD pathology, including neurite outgrowth, synaptogenesis, and long-term potentiation. The linoleic acid derivative 8-[2-(2-pentylcyclopropylmethyl)-cyclopropyl]-octanoic acid (DCP-LA) specifically activates PKC-ε and has been shown to be beneficial for cognitive and molecular pathology in transgenic models of AD. Since transgenic models have many issues when it comes to the drug development process, we have tested the therapeutic potential of DCP-LA in the ferrous-amyloid-buthionine (FAB) rat model, which is a pharmacological AD model that focuses on the role of oxidative stress in the molecular pathology of the disease.
We assessed the effects of DCP-LA on learning, memory, neuronal health, and synaptic density. Male rats received FAB or saline vehicle i.c.v. for 4 weeks via osmotic minipump infusion. There was a decrease in performance for FAB rats in both the learning and memory tasks in the Morris water maze. A single administration of DCP-LA (3mg/kg, i.p.) 24h before water maze training restored performance on both tasks to the level of control animals. Immunostaining for the neuronal marker NeuN was used to determine neuronal health in the hippocampus. There was significant neurodegeneration observed in the CA1, CA3, and dentate gyrus regions of FAB rats compared to all other groups. DCP-LA treatment partially restored the density of healthy neurons, but not to back control levels in the CA1 and CA3. Synaptic density in the hippocampus

was assessed using immunostaining for the synaptic marker synaptophysin. FAB rats exhibited significant loss of synaptic density in all three hippocampal regions tested, which was restored to control levels by DCP-LA treatment.
Together, these data suggest that DCP-LA treatment is able to reverse learning and memory deficits and improve neuronal and synaptic health in a pharmacological rat model of Alzheimer's disease. This suggests that DCP-LA has potential to be used in the human disease, although more research is required to determine key safety data, such as systemic toxicity, optimal dosages, and treatment windows.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.18/V5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Targeting extracellular cyclophilin A in Alzheimer's disease

**Authors: *G. L. SUIDAN**[1], K. WRIGHT[2], N. M. KABLAOUI[3], K. FONSECA[4], R. D. BELL[1]
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**Abstract:** The neurovascular unit (NVU) is composed of endothelium, pericytes, vascular smooth muscle cells, glia and neurons. The NVU modulates blood-brain barrier (BBB) integrity as well as cerebral blood flow (CBF). Clinical evidence and animal studies have implicated BBB dysfunction in several CNS disorders including Alzheimer's disease (AD), cerebral amyloid angiopathy and vascular dementia. Emerging evidence suggests that cerebrovascular dysfunction contributes to cognitive impairment and actually precedes typical biomarkers of AD. Cyclophilin A (CypA) is an abundant isomerase that also plays a role in the initiation of inflammatory processes. Increases in the extracellular pool of CypA (eCypA) have been reported in vasculopathies such as hypertension, myocardial infarction and diabetes. CypA is also present in cerebrospinal fluid of APOE4 carriers and preclinical data in APOE4 transgenic mice showed that elevated CypA damages the BBB. The goal of this study was to provide evidence that eCypA is a relevant target in AD. Using a novel assay to assess CypA levels, we found that plasma cypA is highly elevated in AD patient plasma, a finding that was reproduced in two separate cohorts. We also utilized an amyloid mouse model of AD to investigate the role eCypA in the reduced neurovascular coupling reported in these animals. Here, we show that a two-week treatment with an eCypA inhibitor restored the CBF response to whisker stimulation in AD

transgenic mice. Together, these data indicate that targeting eCypA to promote NVU function may be a therapeutic avenue for improvement of cerebrovascular dysfunction in AD.

**Disclosures: G.L. Suidan:** 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); Stock. **K. Wright:** 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); Stock. **N.M. Kablaoui:** 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); Stock. **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); Stock. **R.D. Bell:** 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); Stock.

**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.19/V6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R01MH107659

**Title:** Identification of a novel small molecule neutral sphingomyelinase 2 inhibitor: Implications for the treatment of Alzheimer's disease (AD)

**Authors: *A. G. THOMAS**[1], M. SALA[6], C. ROJAS[2], A. D. CHAUDHURI[3], S. C. ZIMMERMANN[4], R. RAIS[4], N. J. HAUGHEY[3], R. NENCKA[6], B. S. SLUSHER[5]
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**Abstract:** Brains from AD patients have been shown to exhibit accumulation of ceramide, a bioactive lipid critical for the cellular secretion of exosomes. One major source of ceramide is through the hydrolysis of sphingomyelin catalyzed by neutral sphingomyelinase 2 (nSMase2). Even though transient ceramide increases through nSMase2 plays a role in normal function, chronic upregulation of ceramide has been associated with the pathogenesis of several neurodegenerative disorders including AD, HIV-associated neurocognitive disorders and

multiple sclerosis. Two recent *in vivo* studies carried out by independent laboratories and using different AD models showed that pharmacologic and genetic inhibition of nSMase2 resulted in strong efficacy end points. In one study, GW4869, a prototype nSMase2 inhibitor, inhibited tau propagation from the cortex to the hippocampus in a rapid tau propagation mouse model. In the other, nSMase2-deficient 5XFAD mice compared to wild-type mice exhibited reduced brain exosomes, ceramide levels, tau phosphorylation and improved cognition in a fear-conditioned learning task. While nSMase2 is emerging as an important player in AD etiology, the current armamentarium of nSMase2 inhibitors is inadequate to develop treatments. Currently available inhibitors exhibit low potency ($IC_{50}$'s in µM level), poor solubility, and/or limited brain penetration. In order to address these limitations, we developed a fluorescence-based assay using human recombinant nSMase2 and conducted high throughput screening. Identified hits were optimized using an iterative testing funnel where compounds are evaluated for human nSMase2 inhibitory potency, functional inhibition of exosome release in primary glial cells, cellular permeability, metabolic stability, *in vivo* pharmacokinetics, including brain penetration, and target selectivity. Our early hit optimization effort resulted in MS882, a potent nSMase2 inhibitor ($IC_{50}$=300 nM), able to dose-dependently inhibit exosome release in primary glial cells ($EC_{50}$=1 µM), which was stable in both mouse and human liver microsomes and exhibited a good pharmacokinetic profile, including brain penetration (concentration in brain at 2 h following systemic dosing was >5-fold higher than its nSMase2 $IC_{50}$). MS882 also showed good selectivity over two related enzymes - alkaline phosphatase and acid sphingomyelinase. MS882 is currently being evaluated for efficacy *in vivo*. nSMase2 is a novel therapeutic target that is mechanistically distinct from previous efforts in AD treatment with the potential of addressing disease progression that exploits a newly discovered chemical series of drug-like inhibitors.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.20/V7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** BrightFocus Foundation

Harrington Discovery Institute, University Hospitals of Cleveland

Alzheimer's Drug Discovery Foundation

**Title:** A novel, small-molecule activator of glutamate transporter EAAT2 translation delays disease progression in a tauopathy model of Alzheimer's disease

**Authors: *J. B. FOSTER**[1], F. ZHAO[1], K. HODGETTS[2], C.-L. G. LIN[1]
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**Abstract:** Alzheimer’s disease (AD) is a progressive neurological disease characterized by glutamate dyshomeostasis, amyloid-β plaques, tau-tangles, and progressive loss of cognitive functions. Current therapeutics are limited in efficacy and only provide temporary, palliative care. Therefore, there is need to develop novel therapeutics that can substantially slow or reverse disease progression. Glutamatergic transmission and synaptic concentration are elevated in AD patients. This can lead to synaptotoxicity, amyloid-β deposition, and hyperphosphorylated-tau accumulation of which each can create a feedforward loop where glutamate release is further stimulated exacerbating neuronal damage. Excitatory amino acid transporter 2 (EAAT2) is responsible for clearing glutamate from the synaptic cleft and preventing excitotoxicity. However, many AD patients have reduced expression of EAAT2. We have developed a small-molecule compound series that is capable of increasing EAAT2 expression through a translational induction and previously shown that it has profound efficacy in an amyloid-β AD model. However, tau pathology is also involved in AD. Here, we evaluated the efficacy of an advanced compound in rTg4510 mice that exclusively exhibit tau pathology. We hypothesized that long-term compound treatment will delay disease progression and improve synaptic integrity. rTg4510 mice were treated with LDN/OSU-215111 (10 mg/kg P.O.) beginning at age 2 months and were treated until 4 or 8 months of age. Four-month old compound-treated rTg4510 mice performed significantly better in cognitive tasks (novel object recognition/T-maze), a working memory test (Y-maze), and showed significantly reduced hyper-exploratory behavior. Even at 8 months of age, treated rTg4510 mice appeared to perform better in the Barnes maze and novel object recognition task as well as reduced hyper-exploratory behavior. Consistent with 8-month behavioral data, hippocampal long-term potentiation (LTP) in compound-treated rTg4510 mice was significantly increased. Biochemically, at both time points, treatment partially normalized EAAT2 protein levels and preserved synaptic integrity. This study suggests that modulation of EAAT2 expression is a viable therapeutic for the treatment of AD.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.21/V8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** German Federal Ministry of Education and research Grant FKZ 031A575A

**Title:** Comparing intranasal and intracerebral delivery of mesenchymal stem cells to treat a transgenic mouse model of Alzheimer's disease

**Authors: *L. DANIELYAN**[1], A. STOLZING[2], A. LOURHMATI[1], M. BUADZE[1], K. ARNOLD[3], C. FABIAN[3], H. NGUYEN[4], W. H. FREY, II[5], M. SCHWAB[1]
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**Abstract:** Objectives
In the last decade intranasal administration (INA) of stem cells was proven to be an efficacious non-invasive delivery, targeting and treatment method in preclinical models of brain disorders including Parkinson's disease, stroke, neonatal ischemia, glioma, multiple sclerosis and others. Our previous study demonstrated that intranasal mesenchymal stem cells (MSC) are successfully delivered to the brain in a double transgenic Alzheimers mouse model. However, the therapeutic efficacy of MSCs after INA and the comparison of INA vs. intracerebral transplantation (ICT) remained unexplored.
Methods
Mouse eGFP-MSCs were administered either stereotactically into the hippocampus or given intranasally to 6-month old 3xTg-AD mice. Memory deficit was monitored one week prior and 3 weeks after MSCs transplantation by forced choice alternation T-maze. Tracking of administered stem cells was analyzed immunohistochemically using eGFP antibody in the brains of mice. Brain homogenates were analyzed for the presence of soluble Amyloid beta fragments and synaptophysin as a presynaptic marker.
Results Spatial memory was improved by both ICT and INA of MSCs over the entire time of testing. The Western Blot analysis also showed equal efficacy of INA and ICT of MSCs to increase synaptophysin expression. In contrast, INA of MSCs was more efficacious in decreasing soluble Amyloid beta fragments and in delivery as well as survival of the administered cells in the cortex and hippocampus of 3xTg-AD mice.
Conclusions
In a view of the invasiveness of surgical transplantation and consequently low survival of transplanted cells due to the strong inflammatory response to intracerebral injection, the successful establishment of non-invasive INA methods allowing for repeated cell administration and avoiding inflammation provides an improved strategy for cell-based therapy of central nervous system disorders. Our data strongly support the value of intranasal administration as an efficacious non-invasive method of delivery, targeting and treatment, providing better and sustained survival of stem cells with repeated administration and allowing for the full therapeutic potential of stem cells in the central nervous system.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.22/V9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** CIHR Grant

Wellcome Trust Seed Grant

Alzheimer's Society of Canada Grant

Krembil Foundation Grant

**Title:** Design and optimization of an anti-protein misfolding agent for alzheimer's disease

**Authors: *D. F. WEAVER**, C. BARDEN, K. KESKAR, E. LU, M. REED, M. TAYLOR, Y. WANG, F. WU, S.-P. YANG
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**Abstract:** The pathological hallmarks of Alzheimer's disease (AD) are characterized by clumps of aggregated beta-amyloid (Aβ) ("plaques") and tau ("tangles"), which along with their monomeric forms are thought to be pathologically benign. Sporadic or templated misfolding of these monomeric proteins initiates an oligomerization process to generate intermediate transient oligomeric species that display a multitude of neurotoxic and synaptotoxic effects. We have identified a novel druggable target known as the Common Conformational Motiff (CCM) which is an abnormal protein shape shared by both Aβ and tau that can be exploited to prevent their misfolding and oligomerization. Using the CCM model, a library of 11.8 million compounds was filtered for CNS properties and screened in silico against CCM leading to 3,082 hits. Through hit to lead and lead optimization efforts, we have discovered a novel class of brain-penetrant small molecule entities capable of preventing oligomerization of both beta-amyloid and tau. Efficacy of lead compounds was measured in a variety of biochemical in vitro assays. The structural effect of compounds on tau was measured by time resolved hydrogen-deuterium exchange electrospray ionization mass spectrometry (TRESI-HDX). In vitro absorption-distribution-metabolism-excretion-toxicity (ADMET) data along with mouse pharmacokinetics/ bioavailability (plasma and brain) was collected. Levels of Aβ oligomers were measured in APP/PS1 mouse interstitial fluid by repeated sampling through microdialysis. Levels of tau oligomers in homogenized cortex of the rTg4510 mice were measured by FRET-biosensor cells (tau RD P301S-CFP/YFP). Lead compounds showed anti-oligomerization activity against both Aβ and tau and correlate with structural changes induced in phosphorylated tau. This class of molecules has optimal drug like properties, demonstrating favorable in vitro ADMET, high brain

penetrance and oral bioavailability, and benign in a 44-receptor panel test. A lead compound TRV 301 demonstrates dose dependant reduction of both Aβ and tau oligomers in vivo. In conclusions, we have developed a new class of compounds capable of inhibiting oligomerization of both beta-amyloid and tau proteins. Our small molecules have appropriate pharmacokinetic profiles, able to reach the target tissue, and have demonstrated efficacy in animal models of both Aβ and tau pathologies.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.23/V10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA Grant R01AG038961

NIH/NIBIB Grant R01 EB009041

Focused Ultrasound Foundation grant: "Antibody Delivery Through the BBB Opening in an Alphasynuclein Model"

Swedish Research Council

Alzheimerfonden and Hållstens forskningsstiftelse, Sweden

CIMED, Sweden

**Title:** Targeted brain BRICHOS domain delivery using focused ultrasound-induced blood-brain barrier opening > the treatment of Alzheimer’s disease

**Authors: *C. J. SIERRA SANCHEZ**[1], L. GALAN ACOSTA[3], J. PRESTO[3], P. NILSSON[3], J. JOHANSSON[3], E. E. KONOFAGOU[1,2]
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**Abstract:** The BRICHOS domain is encoded in more than 10 human genes associated with cancer, dementia (BRI2/ITM2b) and amyloid lung disease (proSP-C). Studies have shown that

overexpression of proSP-C or Bri2-BRICHOS delays fibril formation and toxicity of amyloid-β peptide (Aβ) *in vitro* and *in vivo*, which plays a central role in the development of Aβ amyloid plaques, one hallmark of Alzheimer´s disease (AD). BRICHOS domain thus has the potential for treating this disease. It has been revealed, *in vivo*, that overexpression of proSP-C or Bri2-BRICHOS proteins delayed Aβ42 fibril formation in the brain and improved lifespan and locomotor function in *Drosophila* flies. However, in wild-type mice, after intravenous administration, a limited amount of Bri2-BRICHOS was detected in the brain parenchyma, most likely due to a poor passage through the blood-brain barrier (BBB). Therefore the main objective of this study is to increase the BRICHOS domain delivery rate in a safe and non-invasive way, being currently focused ultrasound (FUS)-induced BBB opening the sole technique to achieve noninvasive, transient, and localized brain drug delivery.
In this study, a single-element FUS transducer (center frequency 1.5 MHz) and a pulse-echo transducer (center frequency 10 MHz), used for passive cavitation detection, confocally mounted at the center of the FUS transducer, were used. A pulsed FUS (pulse length 6.56 ms; pulse repetition frequency 5 Hz; duration 2 min; acoustic pressure 450 kPa) was targeted, in the presence of lipid microbubbles, transcranially *in vivo* to the left hippocampus of the mouse brains for trans-BBB delivery of BRICHOS domain. Mice were kept 2 hours after sonication to allow the BRICHOS domain to diffuse to the parenchyma, and then they were sacrificed for assessing the delivery by *ex vivo* immunohistochemistry (IHC) for proSP-C or Bri2 BRICHOS using a primary rabbit anti-surfactant protein-C antibody and permanent Alkaline Phosphatase red for developing the stains. Also, the neuronal marker NeuN was used for assaying possible neuronal BRICHOS uptake. BBB opening was confirmed *in vivo* by $T_1$-w magnetic resonance imaging. The overall brain histology was evaluated by hematoxylin & eosin staining for microscopic damage.
Successfully targeted brain BRICHOS domain delivery was achieved in 6 out of 10 cases. Notably, IHC showed selective uptake of BRICHOS by a specific subset of neurons in the FUS targeted hippocampus section. Microhemorrhages were observed only in two cases. This study indicates that FUS is a safe methodology for targeted brain BRICHOS domain delivery, with a potential promising application in the treatment of AD pathology.

**Disclosures: C.J. Sierra Sanchez:** None. **L. Galan Acosta:** None. **J. Presto:** None. **P. Nilsson:** None. **J. Johansson:** None. **E.E. Konofagou:** None.

**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.24/V11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Grant from UCOST, Government of Uttarakhand, Uttarakhand, INDIA

**Title:** Screening medicinal plants of Uttarakhand, India for BACE inhibitor

**Authors: *A. THAPLIYAL**[1], P. ANTHWAL[1], M. THAPLIYAL[2], N. KUMAR[1], R. CHATURVEDI[3], S. AHMAD[4]
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**Abstract:** Alzheimer ’s disease (AD) is being called a silver tsunami due to the phenomenal increase in number of AD patients and the economic burden it imposes. As per Alzheimer's Association, AD poses a burden of 818 billion US$ and it is suggested that there are about 46.8 million patients worldwide. Many countries, like India, who contribute a big chunk of human population, do not even have the baseline database on the number AD (or dementia) patients. Since several decades now, the most accepted hypothesis for AD with real translation impact is the amyloid beta hypothesis. This hypothesis is well accepted mostly due to work of several investigators including Glenner & Wong, 1984, Beyreuther & Masters, 1991; Hardy & Allsop, 1991; Selkoe, 1991; Hardy & Higgins, 1992.Several pathways are known, several database exist but a cure is elusive. Historically, molecules from plant have contributed a lot to drug development. In our current study we have screened medicinal plants of Uttarakhand, India for BACE inhibitor, which is component of amyloid hypothesis. Several workers have worked on phyto-chemicals but our hypothesis was to identify a fraction of medicinal plant which would have several components instead of single phyto-moiety. The rationale for this thinking was that sometimes a group of phyto-components show better results than a single moiety. This study was done in three parts. First, medicinal plants were listed and a bioinformatics based screening using iGEMDOCK software was carried out. This screening shortlisted about 20 phyto-constituents. On the basis of rationals, pilot experiments were carried out with crude extract of 8 medicinal plants as per Mancini et. al., 2000. Extract of one medicinal plant, *P. kurroa* could inhibit BACE activity. A fresh extract of this medicinal plant was prepared with higher amount of starting material. BACE activity was monitored by fluorescent substrate kit (Abcam ab65357). Here we present our data to confirm that extract of *P. kurroa* can inhibit BACE activity better than known controls *in-vitro*.

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**Poster**

**479. Preclinical Therapeutic Strategies for Neurodegenerative Disease III**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 479.25/V12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** National Natural Science Foundation of China 81571038

**Title:** Involvement of a novel phosphorylation site of BACE1 in amyloidogenic APP processing

**Authors: *Y. ZHENG**[1], H. AN[1], Y. HE[1], J. ZHANG[1], L. DONG[2], X. WANG[1]
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**Abstract:** The β amyloid is generated by sequential cleavage of amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase, and plays a central role in Alzheimer's disease (AD) pathogenesis. BACE1 is the rate-limiting enzyme for the amyloidogenic APP processing. Despite much research, the modifications of BACE1 related to β-secretase activity in AD process remain unclear. In the present study, we discovered a novel phosphorylation site of BACE1, which was detected by a specific antibody recognizing phosphorylated threonine (Thr) 252 site of BACE1. The phosphorylated BACE1 was found increased in hippocampus and cortex of an AD transgenic mouse model (5XFAD) at 1.5 months old, at which Aβ generation was increased. Further, we designed and constituted plasmids carrying $BACE1^{WT\text{-}GFP}$, $BACE1^{T252A\text{-}GFP}$ (Thr252 was replaced by alanine, resulting in deficiency of threonine phosphorylation), $BACE1^{T252D\text{-}GFP}$ (Thr252 was replaced by aspartic acid, resulting in mimics phosphorylation of threonine), respectively, and performed overexpression study in 293APPsw cells, which is a cell line stably overexpressing APPsw mutant, to investigate the function of the phosphorylated BACE1 in Aβ production. As expected, $BACE1^{WT\text{-}GFP}$ and $BACE1^{T252D\text{-}GFP}$ overexpression promoted Aβ generation in the cell line, while $BACE1^{T252A\text{-}GFP}$ had no this effect, suggesting that the phosphorylation site of BACE1 is associated with its β-secretase activity. Intriguingly, further study revealed that the β-cleavage function of BACE1 in 5XFAD/$BACE1^{-/-}$ mice was rescued by stereotactic injection of lenti-$BACE1^{WT\text{-}GFP}$ in hippocampus, but not by lenti-$BACE1^{T252A\text{-}GFP}$, implying that the phosphorylated BACE1 at Thr 252 site can determine the β-secretase activity of BACE1 in AD brain. In conclusion, the study provide a new insight into amyloidogenic APP processing and AD therapeutic implications.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.01/V13

**Topic:** C.03. Parkinson's Disease

**Support:** Ontario Graduate Scholarship

Mitacs

Michael J. Fox Foundation

Schulich School of Medicine and Dentistry

**Title:** Alteration of gene expression in brain tissue samples from living Parkinson's disease patients

**Authors: *S. M. BENOIT**[1], H. XU[2], S. SCHMID[3], R. ALEXANDROVA[4], G. KAUR[4], B. THIRUVAHINDRAPURAM[4], M. O. HEBB[5]
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**Abstract: Introduction:** Differential gene expression in the central nervous system (CNS) of living Parkinson's disease (PD) patients has not been previously reported and may offer critical biomarkers to define pathogenic mechanisms, new therapeutic targets, early diagnosis and disease progression. The current objective was to examine the transcriptome for gene expression alterations using RNA isolated from brain specimens in living PD and control patients. **Methods:** Total RNA was extracted from cortical biopsies in 6 patients with PD and 6 healthy controls and sequenced on the Illumina HiSeq 2500 platform using a stranded paired-end protocol. Reads, totaling approximately 90 million per sample, were trimmed to remove adapters and low quality bases, then aligned to the human genome (Hg19) using TopHat (v.1.8). Raw counts were generated using HTSeq (v.0.6.1p2); and analyzed for differential expression using edgeR (v.3.8.6). Pathway enrichment analysis was performed using the analysis tools from the Gene Ontology Consortium (http://www.geneontology.org/). **Results:** At an FDR threshold of <0.05, 763 differentially expressed genes were identified, with 347 upregulated and 416 downregulated in PD. Twenty-five of these genes had >4-fold change in expression. Genes commonly associated with or known to cause monogenic PD, such as SNCA, Parkin, PINK1 and LRRK2 showed no differential expression. The expression of Glial-derived neurotrophic factor, a potent neuroprotective and putative therapeutic agent, was significantly reduced in PD samples. Matrix-metallopeptidase 9, which has been positively linked to PD in single nucleotide polymorphism studies, and Interleukin-10, an anti-inflammatory cytokine with a highly polymorphic promoter also associated with PD, were also among several dysregulated genes with experimental associations to neurodegenerative disease. Further, pathway analysis showed enrichment of immune and inflammatory response processes, lending further evidence to findings of dysregulation of inflammatory processes in PD. **Conclusions:** To our knowledge this is the first demonstration of differential CNS gene expression in living PD patients. Alterations in gene expression in approximately 4% of the detected genes offer a wealth of data with potential to identify genetic biomarkers that may facilitate diagnosis and treatment for PD and other neurodegenerative diseases.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.02/V14

**Topic:** C.03. Parkinson’s Disease

**Support:** Michael J. Fox Foundation for Parkinson’s Research Dyskinesia Challenge

Spanish Ministry of Economy and Competitivity: Project SAF2014-57160-R

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**Title:** Associations between single nucleotide polymorphisms in the mTOR pathway with early onset and severity of L-DOPA induced dyskinesia in Parkinson's disease patients

**Authors: *N. MARTIN-FLORES**[1], *N. MARTIN-FLORES[1,2], R. FERNANDEZ-SANTIAGO[3,4,5], F. ANTONELLI[4], C. CERQUERA[4], V. MORENO[4], M. J. MARTÍ[4,3,5], M. EZQUERRA[3,5,4], C. MALAGELADA[1,2]
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**Abstract:** Parkinson’s disease (PD) is the second most common neurodegenerative disorder and is characterized by the degeneration of certain neuronal populations in the central and peripheral nervous system. Although there is no therapy to halt or delay neurodegeneration, there are pharmacological or surgical approaches that treat the symptoms and improve the patients’ quality of life. To counteract striatal dopamine deficiency and treat PD symptoms the most effective drug is levodopa (L-DOPA). L-DOPA is the precursor of dopamine and its administration enhances striatal dopamine levels. However, chronic treatment with L-DOPA triggers other motor complications, including dyskinesia and motor fluctuations. L-DOPA-induced dyskinesia (LID) is one of the most disabling problems for PD patients. Currently there is no method to predict which PD patient will develop LID, whether it will be an early or a late LID onset or whether LIDs will be severe and incapacitating. One strategy to identify possible molecular markers to predict L-DOPA treatment outcome involves the screening of single-nucleotide polymorphisms (SNP) in crucial signaling pathways associated to PD pathogenesis. mTOR signaling is one of these pathways. Genetic variations in the mTOR pathway could explain the differential sensitivity to L-DOPA in PD patients. For this reason, here we investigated potential associations between genetic variations in the genes of the mTOR pathway and the onset and

severity of LIDs in patients with PD. We selected 64 SNPs from 57 genes in the mTOR pathway. After microarray genotyping we filtered out SNPs, resulting in the final number of 54 SNPs that were included in the association analysis of single SNPs or their combinations. The whole cohort of study consisted in 1,819 subjects including 898 PD cases and 921 unrelated healthy controls. A total of 401 of the 898 PD cases had complete L-DOPA treatment and LID data registered in their clinical histories. Genotypic associations were computed using the SNPStats software and combinations of SNPs and epistatic combinations were calculated using the SNPsyn and the MDR softwares. Here, we found new associations between the early appearance and the severity of LIDs with SNPs in components of the mTOR pathway. We have detected both single SNPs associations and epistatic interactions of SNPs that could predict the appearance or severity of LIDs. The results in this study will be used to design a diagnostics test to predict PD patients susceptibility to develop early LID onset and LID severity, with the overall goal to prevent/delay LID appearance and therefore, to improve PD patients' quality of life.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.03/V15

**Topic:** C.03. Parkinson's Disease

**Support:** R00 ES024570

**Title:** Parkinson's disease associated alterations in the DNA modifications, 5-methylcytosine and 5-hydroxymethylcytosine

**Authors: *A. I. BERNSTEIN**, S. VANOEVEREN
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**Abstract:** Parkinson's disease (PD) is the second most common neurodegenerative disease in the US. Pathological hallmarks of PD include the degeneration of the nigrostriatal dopaminergic pathway and other monoaminergic regions and the formation of Lewy bodies, abnormal cytoplasmic inclusions. While a small percentage (5-10%) of PD cases are monogenically inherited, the large majority of cases of PD are sporadic. Etiology of sporadic PD is thought to involve a combination of and interaction between both genetic and environmental factors. It is possible that these genetic and environmental factors converge upon the epigenome. Epigenetic modulations could imprint dynamic environmental experiences on the genome, resulting in stable alterations in phenotype. In fact, recent work suggests a role for regulation of the

epigenome in PD. For example, aberrant gene methylation of PD-associated genes has been observed in post-mortem PD brains. In addition, expression of α-synuclein has been shown be regulated by promoter methylation and α-synuclein sequesters the DNA methyltransferase DNMT1 away from the nucleus, resulting in DNA hypomethylation. Therefore, we hypothesized that specific alterations in DNA modifications are associated with PD and that these changes alter gene expression in disease relevant gene networks, thereby increasing susceptibility to PD. To test this, we profiled the DNA modifications, 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC), and the transcriptome in human postmortem brain tissue from mid-stage PD patients, late-stage PD patients and controls. To capture changes that may occur prior to the onset of pathology, we profiled both cingulate and parietal cortex, as these regions show pathology in mid and late stage disease, respectively. Previous epigenome-wide association studies for PD have not incorporated 5hmC or correlated epigenetic changes to transcriptional changes. DNA modifications were profiled using the Illumina EPIC array, paired with bisulfite and oxidative bisulfite conversion for detection of 5mC and 5hmC, respectively. The transcriptome was profiled by RNA-Seq. We identified differentially methylated and hydroxymethylated regions associated with PD diagnosis and disease stage and incorporated this data with gene expression data from RNA-Seq. In addition, we incorporated known disease associated SNPs. Network analysis of these genes implicates specific gene networks in the etiology of PD and identifies novel mechanisms of epigenetic regulation in PD.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.04/V16

**Topic:** C.03. Parkinson’s Disease

**Support:** MJFF Grant 8934

Mayo Clinic

**Title:** DNA methylation, gene expression and splicing analysis for Parkinson’s disease blood biomarker discovery

**Authors: *A. R. HENDERSON-SMITH**[1], B. MEECHOOVET[1], A. L. SINIARD[1], E. DRIVER-DUNCKLEY[2], T. DUNCKLEY[3], M. J. HUENTELMAN[1]
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**Abstract:** Parkinson’s disease (PD) is a progressive neurodegenerative disorder, diagnosed only at an advanced disease stage, by a series of motor deficits that manifest over years or decades. Aberrant epigenetic modifications, including hypomethylation of α-synuclein in PD, exist across a range of diseases, from cancer to schizophrenia, and are non-invasively detectable in many body fluids and blood tissue as markers of disease.
We aimed to characterize DNA methylation and gene expression patterns in blood from PD patients and matched healthy controls to identify disease-specific biomarkers that may be used to aid earlier, more accurate disease diagnosis and tracking of disease progression.
Whole-blood samples were collected from PD patients and healthy controls, one for DNA methylation detection and one for mRNA sequencing. DNA methylation sites were probed with the Illumina Infinium HumanMethylation450 BeadChips. We used the Illumina HiSeq2000 platform for mRNA sequencing and performed separate and integrated analyses of differential expression and DNA methylation.
PD methylation profiles are readily distinguishable from healthy controls, even in whole blood DNA samples. Differential expression analyses of mRNA-seq data identified global changes in gene regulation, including overall gene expression levels and expression levels of specific transcript splice variants. Combined methylation quantitative trait loci analyses (meQTL) identified cis-acting meQTLs associated with differential expression of proximal loci.
Establishing clear patterns of altered disease-specific DNA methylation, RNA expression and processing, and meQTL analyses from whole blood, a non-invasive tissue collection option, provides increased promise for the development of a molecular biomarker for PD with sufficient sensitivity and specificity to aid in the diagnosis and tracking of this disorder.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.05/V17

**Topic:** C.03. Parkinson’s Disease

**Support:** Croatian Science Foundation (LYSOGENE PD-9386)

**Title:** Genetic mechanisms of lysosomal dysfunction in Parkinson’s disease - the effect of novel variants on alpha-synuclein accumulation

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**Abstract:** Accumulation of misfolded proteins in the brain is the main pathological hallmark of neurodegenerative diseases, including Parkinson's disease (PD), suggesting that inadequate clearance of aggregation-prone proteins plays an important role in the disease pathogenesis. Studies on the rare inherited forms of PD have highlighted disturbed alpha-synuclein (aSyn) clearance through the autophagy-lysosomal pathway (ALP) as a key mechanism leading to PD. In order to characterize the putative underlying genetic mechanisms leading to ALP dysfunction in PD, we performed comprehensive analysis of genetic variants in ALP genes in PD patients. The study included 70 PD patients and 25 healthy control subjects. Genetic variants were ascertained using the custom LYSOGENE targeted next-generation sequencing (NGS) panel, containing a comprehensive set of 440 ALP related genes, as well as genes previously implicated in familial forms of PD. In order to assess the technical variability, we analyzed the samples using the SureSelect (Agilent) and Nextera Custom Enrichment (Illumina) library preparation kits. We identified a significant number of ALP gene variants among PD patients when compared to control subjects, with 815 variants pertaining to 290 genes present exclusively in PD patients. These variants were involved in over 50 biological processes, with the greatest enrichment observed in categories of lysosome organization, organic substance transport, abnormal myelination and sphingolipid metabolism. In contrast, variants found exclusively in healthy subjects were not related to specific biological pathways. Based on the NGS data, we selected genes ARSD, GALC, IDUA and LRBA with the most over-represented genetic variants in PD patients and investigated their effects on lysosomal impairment, aSyn accumulation and neurotoxicity using the neuroblastoma SH-SY5Y cell lines stably expressing human alpha-synuclein. The results were compared to the effects of the knock-down of a known lysosome-related gene, ATP13A2, which causes a rare autosomal recessive form of juvenile-onset atypical Parkinson disease (PARK9). Our knock-down experiments confirmed the link between lysosomal impairment and aSyn accumulation. In total, our results strongly suggest that specific variants in ALP genes may contribute to lysosomal dysfunction in PD. Furthermore, these genetic variants may modulate aSyn clearance, thus promoting the PD pathology.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.06/V18

**Topic:** C.03. Parkinson's Disease

**Support:** Michael J. Fox Foundation

NIH/NIEHS 1R01ES024745

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R21CA17553

**Title:** NLRP3 polymorphism associated with a decreased risk of Parkinson's disease impacts NLRP3 protein life cycle

**Authors: *K. VON HERRMANN**, L. A. SALAS, E. M. MARTINEZ, W. W. FENG, W. F. HICKEY, A. N. KETTENBACH, B. C. CHRISTENSEN, S. L. LEE, M. S. FELDMAN, M. C. HAVRDA
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**Abstract:** Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by debilitating motor symptoms and affects 1.5-2% of individuals over the age of 60. The pathophysiology of PD, characterized by loss of dopaminergic neurons in the *substantia nigra* and accumulation of alpha-synuclein immunoreactive protein aggregates has long been associated with neuroinflammation. The NLRP3 inflammasome is a catalytic multiprotein complex capable of initiating inflammation in response to non-pathogenic cellular stress. Our ongoing studies, and reports by others, support a role for *NLRP3* in PD-associated neuroinflammation and neurodegeneration; elevated NLRP3 is also observed in the central nervous system of patients with Alzheimer's disease. We observed increased NLRP3 expression levels in dopaminergic neurons in post-mortem tissues from PD patients, and recently identified genetic variations in *NLRP3* by interrogating exome sequencing data obtained from the ongoing Parkinson's Progression Markers Initiative. One *NLRP3* variant, single nucleotide polymorphism (SNP) rs7525979, was found to be associated with a decreased risk of classical PD. The SNP could also differentiate patients with classical PD from patients with a form of non-classical parkinsonism identified clinically as "scans without evidence of dopaminergic deficit (SWEDD)." Synonymous SNPs, like *NLRP3* variant rs7525979, occupy the third codon position and do not impact the amino acid sequence. Although still poorly understood, it is thought that dysregulation at the level of translation, likely resulting from tRNA availability, mRNA stability, mRNA structure, and/or mRNA splicing, impacts the protein life cycle at levels ranging from translation efficiency to proteosomal degradation. Having identified the synonymous *NLRP3* SNP rs7525979 to be significantly associated with a reduced risk of PD, we conducted mechanistic studies to determine how rs7525979 may confer resistance to the disease. We assessed the impact of the synonymous SNP on properties of NLRP3 protein and found that the presence of the SNP increased protein half-life in association with reduced solubility and alterations in ubiquitination. We also characterized the impact of rs7525979 on the NLRP3 interactome using LC/MS techniques and found that the presence of the SNP resulted in differential interactions with key mediators of protein translation, folding, and degradation. Findings from these studies highlight the potential of synonymous SNPs to impact proteins and

provide a foundation for studies to determine whether modification of inflammasome function can impact the progression of PD.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.07/V19

**Topic:** C.03. Parkinson’s Disease

**Support:** AADC at Barrow Neurological Institute

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NIH P30AG010161

**Title:** Basal forebrain histone deacetylase dysregulation in Parkinson’s disease with and without dementia

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**Abstract:** Histone acetylation is an epigenetic process involved in gene expression and cell survival, and is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Histone acetylation imbalance is believed to play a pathogenic role in neurodegenerative diseases, including Parkinson’s disease (PD). Dysregulation in histone acetylation has been reported to occur in select brain regions including the midbrain region associated with PD. Whether the region of the basal forebrain (BF) containing the cholinergic neurons that projects to the entire cortical mantle, which plays a role in memory and attention and undergoes selective degeneration in patients with PD, displays histone dysregulation remains unknown. Here, we determined whether histone acetylation alterations occur in PD patients with (PPD) and without dementia. Protein levels of HDACs, the enzymes involved in chromatin condensation and gene transcript repression, were examined in the cholinergic BF in subjects with a pre-mortem clinical diagnosis of non-cognitive-motor impairment (NCMI, n=12), PD (n=10) and PDD (n=12) using quantitative immunoblotting. Western blot analysis revealed that HDAC1 levels in the BF were significantly upregulated in PD and PDD compared to NCMI subjects ($p = 0.001$), but not different between PD and PDD. Conversely, levels of HDAC2,

HDAC3, HDAC4 and HDAC6 were stable across the clinical groups examined. Furthermore, HDAC1 values correlated negatively with age of disease onset ($r=-0.6$, $p < 0.05$) and positively with disease duration ($r=-0.6$, $p < 0.05$) in both PD and PDD. These data suggest that HDAC1 levels are increased in the BF region containing cholinergic neurons in PD and PDD and, may play critical role in BF cholinergic neuronal degeneration in PD subjects with and without dementia.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.08/V20

**Topic:** C.03. Parkinson’s Disease

**Support:** Helis Fundation

MSCRF fellowship

NIH (R37 NS047344)

**Title:** Single nuclei RNA-seq analysis of dopaminergic neuron degeneration

**Authors: *Y. ZHU**[1,2], S. S. KARUPPAGOUNDER[1,2], V. L. DAWSON[1,2], T. M. DAWSON[1,2], G.-L. MING[1,2,3,4,5], H. SONG[1,2,3,5]
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**Abstract:** Progressive degeneration of dopaminergic (DA) neurons underlies the pathology of Parkinson’s disease. Understanding the progressive degeneration process is fundamental in the understanding of the pathology, identification of disease biomarkers, as well as the designing of therapeutic targets for intervention. However, defining the progressive events of molecular changes in the small number of affected DA neurons is challenging, and can be significantly confounded by cell type heterogeneity in the surrounding region and even among different types of DA neurons. The relatively small number of DA neurons also limits the throughput of biochemical and molecular analysis. Here we examined the process of DA neuron degeneration using single-cell transcriptomics analysis.A major challenge for single-cell transcriptomics is to obtain consistent single-cell information from complex tissue with limited technical variation. We compared two approaches: single-cell RNA-seq (scRNA-seq) and single-nuclei RNA-seq (snRNA-set). First, we used a mouse model with Dat promoter-driven expression of H2b-GFP as

a genetic marker to identify DA neurons by nuclear expression of GFP. Given the high correlation of average gene expression between single nuclei and of single cells, we found that the snRNA-seq from adult tissue seemed to have minimal technical variability, and is therefore the preferred approach. Using the snRNA data acquisition that we established, several hundred DA neurons have been profiled from normal adult mice to study the physiological variation of gene expression profiles in the population of DA neurons. In contrast to the common belief of the existence of distinct types of DA neurons, we found a rather gradual change in transcriptomic profiles. Using known markers of region-specific DA neurons, we observed a segregation of transcriptomes from principal components analysis that reflected a spatial transition from the Ventral Tegmental Area (VTA) to Substantia Nigra Compacta (SNC). This analysis highlights the resolution of our approach and the lack of bias towards artificial segregation with preselected markers, providing a platform for investigating the molecular basis of why SNC DA neurons are selectively sensitive to neurotoxins. To investigate the degeneration of DA neurons in pathological conditions, we have collected a few thousand cells from different time points after MPTP treatment in adult mice. We hope that additional analysis and validation will reveal the holistic transcriptomic landscape underlying degeneration, allowing for the identification of new biomarkers as well as novel pharmaceutical targets for disease intervention.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.09/V21

**Topic:** C.03. Parkinson’s Disease

**Support:** Thousand Young Talents Program

**Title:** Impaired temporal working memory in early stages of Parkinson's disease and atypical parkinsonism

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**Abstract: Background:** The ability to arrange thoughts and actions in an appropriate temporal order is fundamental to complex behavior from speech production to action planning. Deficits in temporal working memory (WM) have been observed in Parkinson’s disease (PD) and other brain disorders in both verbal and nonverbal behaviors. This study tested two hypotheses: (a) that the manipulation of temporal order is selectively impaired but the maintenance of temporal order

is intact in medicated nondemented patients with PD or atypical parkinsonism (APS); (b) that dopamine does not improve the manipulation of temporal order in PD patients. **Methods:** Participants were 41 nondemented patients with mild-to-moderate PD (23 females, age 53-76 yrs, education 13.1 yrs, H-Y 1-3, UPDRS III 22.1), 13 nondemented patients with APS (5 females, age 52-77 yrs, education 13.8 yrs, H-Y 1-3, UPDRS III 22.6; including Parkinson dystonia syndrome N=9, multiple system atrophy N=2, progressive supranuclear palsy N= 1, corticobasal degeneration N=1, dementia with Lewy bodies N=1) and 33 matched healthy elderly adults (20 females, age 53-76 yrs, education 13.2 yrs). All patients were on their regular antiparkinson medications. PD patients were further separated according to their ON (N=19, levodopa equivalent daily dose, LEDD 368.6mg) and OFF periods (N=22, LEDD 328.8mg). APS patients were not separated because they did not respond as well to dopaminergic agents. Each participant underwent a digit forward test, in which participants recalled randomly presented digits in their order of presentation (maintenance only), and a digit ordering test, in which participants had to recall randomly presented digits in ascending order (reordering, manipulation). **Results:** Preliminary analysis on test scores (max. 12 for both tests) revealed a main effect of Test ($F=72.9$, $p<0.001$) and an interaction of Test and Group ($F=6.7$, $p<0.01$). Namely, all groups showed a behavioral cost of reordering (ordering<forward). Compared with healthy control subjects, both PD and APS patients performed worse in the digit ordering test, but not in the digit forward test . Further analysis compared PD patients in ON and OFF periods and revealed similar behavioral costs . The cost of reordering was not correlated with LEDD or levodopa actual dose. **Conclusion:** Our findings suggest that the manipulation of temporal order was selectively impaired in PD and APS, but the maintenance were well preserved. More importantly, dopamine may have limited effects on temporal WM. This study is still going on and we will present data from an even larger sample of PD and APS patients during the conference.

**Disclosures:** **Z. Ye:** None. **J. Ma:** None. **S. Ma:** None.

**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.10/V22

**Topic:** C.03. Parkinson’s Disease

**Support:** NPF Grant

**Title:** Does amyloid-beta affect neuroinflammation and cognitive performance in Parkinson's disease?

**Authors: *C. M. GHADERY**[1,2], Y. KOSHIMORI[1,2], J. KIM[3,2], S. COAKELEY[4,2,5], M. HARRIS[5], L. CHRISTOPHER[6,2], P. RUSJAN[5], A. LANG[7], S. HOULE[5], A. STRAFELLA[8,2,7]

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**Abstract: Objective:** To investigate potential interactions between microglial activation and amyloid-β in the brain using positron emission tomography (PET) in Parkinson's disease (PD) with normal and impaired cognitive function. **Background:** Microglia, activated due to neuroinflammation, may play an important role in disease development and progression. A more rapid cognitive decline has been linked to higher amounts of beta-amyloid. Amyloid- β may promote microglial activation and further disease progression. **Methods:** We included 17 PD patients, 11 PD patients with mild cognitive impairment (MCI) and 11 healthy controls (HCs) to assess the impact of amyloid-β in the brain with [$^{11}$C] Pittsburgh compound B (PIB) on microglial activation using the translocator protein 18-kDa (TSPO) radioligand [$^{18}$F]-FEPPA. PIB distribution volume ratio (DVR) was measured in cortical and subcortical regions. A DVR of 1.2 was set to divide each brain region into PIB-positive or PIB-negative. FEPPA total distribution volume ($V_T$) values were compared for each brain region to evaluate the effect of PIB positivity while adjusting for TSPO rs6971 polymorphism (which is implicated in differential binding affinity). **Results:** Preliminary analyzes revealed a significant main effect of PIB positivity in the striatum ($F_{(2, 32)}$= 5.9, p = 0.006). Besides the striatum (p=.019), the dorsolateral (p=.012) and prefrontal cortex (p=.002) as well as the temporal (p=.004) and frontal lobe (p=.006) showed a significant interaction effect. In these regions, the PD-MCI group had significantly higher FEPPA $V_T$ if PIB-positive. In the frontal lobe, this difference was also seen in the PD group (p=.011). Further, PIB-positive PD-MCI patients showed significantly higher FEPPA $V_T$ than PIB-positive HCs in the striatum (p=.019), temporal (p=.012) and frontal lobe (p=.031) as well as significantly higher $V_T$ than PIB-positive PDs in the striatum (p=.028), prefrontal cortex (p=.004) and temporal lobe (p=.011). **Conclusions:** Our results indicate an interaction between amyloid-β and microglial activation in PD. Further investigations are necessary to evaluate if microglia activation affects disease progression or develops as a protective response.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.11/V23

**Topic:** C.03. Parkinson's Disease

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Parkinson Disease Foundation

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**Title:** Hemispheric-specific neuropsychological tests in stage I early-onset Parkinson's disease (EOPD) as a predictor for disease progression

**Authors:** *K. M. LE[1], ***K. M. LE**[1], B. MULLEN[1], K. VENKITESWARAN[1], M. SUBRAMANIAN[1], S. RAVI[2], D. WAGNER[1], S. SWAMINATHAN[1], K. ANANTHAKRISHNAN[1], M. IBRAHIMI[1], J.-L. WANG[1], P. ESLINGER[1], T. SUBRAMANIAN[1]
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**Abstract:** Idiopathic Parkinson's disease (PD) begins in vast majority of patients with unilateral symptoms (Hoehn Yahr Stage I). There is a latent period of an average of 5 years before such patients advance to stage II disease (bilateral Parkinsonism). Most stage I disease patients do not have any evidence of cognitive decline in routine standardized tests. However, sophisticated neuropsychological testing has reviewed subclinical mild deficits. We tested whether hemispheric-weighted neuropsychological tests can differentiate between stage I PD versus stage II PD and predict disease progression. We enrolled 54 subjects in stage I EOPD (age >40 and <60), who are left hemisphere dominant on language functions, verified by right-handedness (Edinburgh handedness scale >0.7), not moderately depressed (BDI-II < 23), and who lack signs of mild cognitive impairment (MOCA >26). The standard mental rotation test(MRT) was administered along with a verbal fluency (VF), mirror tracing, California verbal learning test, tactile performance test, picture vocabulary (PV), design fluency, and visual reproduction every 3-6 months until they reach stage II of the disease as clinically defined by the UPDRS motor sub-scores of bilateral definitive presence of tremor, bradykinesia and rigidity. Most subjects were medication naïve at their first visit and had an overnight drug washout in the practically defined (off) period for their UPDRS assessments. Our results show that there was a distinct difference in MRT score between male and female subjects as suspected from the literature ($p=0.041$). However in both sexes the MRT score were lower than historical controls' data. In right-handed EOPD men with disease onset on the left side of the body , MRT scores were substantially lower than in EOPD male subjects who had symptom onset on the right side of the body ($p=0.064$). Further, upon repeated testing, subjects who developed symptoms in the postural instability and gait domains on the UPDRS part-III had lower MRT scores in both sexes, regardless of the body side of motor symptoms. Dopaminergic treatment did not influence MRT scores. In the PV task, male right onset and left onset did not exhibit a difference in test scores.

However, female right onset did worse than their left onset cohort (p = 0.131). In the DF task, there was no notable difference between the two cohorts for the first 2 conditions, however in the third condition, both female and male left onset subjects did worse than their right onset counterparts (p =0.141 male, p = 0.113 female). These findings suggest that these hemisphere-weighted tests can be a powerful predictor of disease progression in EOPD.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 480.12/V24

**Topic:** C.03. Parkinson’s Disease

**Title:** Handwriting and effector independence in individuals with Parkinson's disease

**Authors: D. L. OLIVEIRA**, R. GIMENEZ, R. B. S. C. GARBUS, C. C. G. ALONSO, R. C. MARINHO, S. M. S. F. FREITAS, *R. S. PIRES
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**Abstract:** Parkinson's disease (PD) is a neurodegenerative disorder that promotes tremor, rigidity, bradykinesia, postural instability and micrographia. Micrographia has recently contributed to the diagnosis of the disease. However, the mechanisms underlying micrographia remain to be investigated. Therefore, our aim was to investigate handwriting through the effector independence of individuals with PD. A cross-sectional study was carried out with PD individuals (n = 14, 9 females and 5 males, aged 52 to 82 years) in Hoehn and Yahr stages I to III with micrographia identified by Unified Parkinson's Disease Assessment Scale (UPDRS, item 8), right-handed, according to the Edinburgh inventory. Participants in the control group (n = 14) were matched with respect to gender and age. The individuals wrote the letter "l" 8 times (8 loops) with the right and left hands, with the normal and altered grips. Five trials were performed in each condition and the order was randomized across condition. The experiments and data analyzes were made with a digitizing table, a computer and "Movalyzer Neuroscript" program. The sampling rate was 100 Hz. The “x” and “y” coordinate data were filtered using the low-pass Fourier Fast Transform (FFT) filter of 12 Hz. The unit of analysis was the stroke (segment between two points characterized by crossing zero at velocity). We performed analysis of variance (ANOVA) for repeated measures for comparison between different effectors and groups, involving the following dependent variables: absolute size and absolute mean velocity. Post-hoc analyzes with Bonferroni adjustment were used when appropriate. The alpha value was maintained at 0.05. Our data revealed that PD individuals had the absolute size smaller than the

control group in all task conditions, hand [F (1; 26) = 6.102, p = 0.020, ηp² = 0.190], grip [F (1 ; 26) = 9602, p = 0.005, ηp² = 0.270] and group [F (1; 26) = 4.099 p = 0.05, ηp² = 0.136]. In relation to the absolute mean velocity, PD individuals were slower than the control group [F (1; 26) = 4,742 p = 0.04, ηp² = 0.154], characterizing bradykinesia. Thus, our data revealed that micrographia is present in PD individuals, independently of the effector used, suggesting that the disfunction is more associated with central control (central nervous system) than peripheral components (muscle rigidity).

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

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**Topic:** C.03. Parkinson’s Disease

**Support:** MOST 106-2218-E-182-003

CMRPD1G0041

EMRPD1F0321

**Title:** The locomotion automatization under cognitive load in Parkinson disease

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**Abstract:** Reduced locomotion automatization is one of the important sign for Basal Ganglia disorder which could explain the Freezing of gait (FOG) for people with Parkinson Disease (PD). In early stage of PD, the de-automatization might be compensated by switching the level of cognitive control for non-freezing patients. This study hypothesized that de-automatization could be detected in early stage non-freezing PD patients in dual task condition while the cognitive resource is competed. Methods: Sixteen individuals with diagnosed PD and 15 healthy controls were recruited. The subjects in PD group were non-freezers with the Modified Hoehn & Yahr between 1 to 2.5. Subjects walked in an instrumented pressure mat at a self-select speed in both single and dual task conditions. In the dual task walking test, a calculation dual task was

provided during walking. The gait speed, step length and the cognitive performance (accuracy, and reaction time) were analyzed for both single and dual task conditions. Results: In terms of cognitive performance, the composite score of accuracy and reaction time were lower in PD group than in control group only during the dual task condition (p=.018). In terms of gait performance, the PD group showed slower gait speed and shorter step length during both single and dual task conditions (p,.05). Conclusion: The cognitive performance in the dual task condition could be an indicator of de-automatization in early stage of PD before FOG developed. Factors other than de-automatization, such as poor balance and postural control, could also explain the decreased gait performance in non-freezing PD patients.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

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**Title:** Biophysical properties of the hyperdirect pathway necessary to match clinical cortical evoked potentials from subthalamic deep brain stimulation

**Authors: *K. GUNALAN**, C. C. MCINTYRE
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**Abstract:** Deep brain stimulation (DBS) of the subthalamic region is an established clinical therapy for the treatment of late stage Parkinson’s disease. Direct stimulation of the hyperdirect pathway, which consists of a special subset of corticofugal axons originating from layer V pyramidal neurons that send an axon collateral to the subthalamic nucleus (STN), has been extensively linked to therapeutic benefit in experimental studies. One experimental measurement used to evaluate hyperdirect activation is the recording of cortical evoked potentials generated by subthalamic DBS. In humans, these evoked potentials have a very fast component (R1) that

occurs ~1 ms after the stimulus pulse, as well as a slower component (R2) that reaches its peak in ~5 ms. R1 is typically assumed to arise from antidromic invasion of the hyperdirect layer V pyramidal neurons, while R2 is assumed to arise from intracortical synaptic activity. To address these assumptions, we used a detailed patient-specific DBS model of hyperdirect pathway activation. We reconstructed the hyperdirect pathway using tractography from diffusion-weighted images. Each of the 1000 streamlines were then modeled as a multi-compartment cable structure. The voltage distribution generated by the DBS electrode was calculated using a finite element method, this voltage distribution was used to stimulate the model axons, and the response of the axons to DBS was quantified. The model system allowed us to evaluate conduction times from activation of the hyperdirect collaterals in the STN to arrival of the action potentials in cortex. We compared the conduction times for small (5.7 μm), medium (10.0 μm), and large (15.0 μm) diameter corticofugal axons. Only the 15.0 μm models could generate a R1 that coincided with clinical measurements of ~1 ms, but histological measurements suggest that axons of that size are extremely rare in the internal capsule. Given the expected diameter distribution of the hyperdirect pathway, R1 and R2 may actually represent a combined continuum of antidromic invasion of cortex, where the experimentally recorded waveform is the result of interacting field potentials generated by neurons with small, medium, and large diameter axons.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** C.03. Parkinson’s Disease

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NIH/NICHD Grant T32 HD007434

**Title:** Differences in neural activity during motor imagery in people with Parkinson disease with and without freezing of gait

**Authors: *P. S. MYERS**, M. E. MCNEELY, G. M. EARHART
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**Abstract: Background:** Gait is impaired in people with PD, especially those with freezing of gait (FoG), and exercise improves gait speed. Neural mechanisms behind exercise-induced gait benefits remain unclear in PD with (FoG+) and without (FoG-) FoG. Motor imagery (MI) and motor execution neural networks overlap, and MI has been used with neuroimaging to understand mechanisms contributing to motor behaviors. Activity in the cerebellum (CBLM) may differentiate FoG+ and FoG- given differences in connectivity with other brain regions. Motor regions such as primary motor (M1) and premotor (PMC) cortices may also differentially change with exercise in FoG+ and FoG-.
**Methods:** We examined neural activity during MI before (pre) and after (post) an exercise program. Participants underwent pre and post MRI scans and motor (MDS-UPDRS-III) and gait testing "off" medication. Functional scans had 4 tasks intermixed: MI of forward gait (MI-FWD), MI of backward gait (MI-BWD), MI of standing (MI-SD), and rest. Participants walked across a GAITRite mat FWD and BWD to assess gait speed. Self-reported freezing was used to separate FoG+ (n=14) and FoG- (n=27). MRI data were processed with BrainVoyager QX. Regions of interest were traced by hand for bilateral CBLM, M1, and PMC. We extracted beta weights for each task from each region and normalized to rest. Pre and post gait speed ($\alpha<.05$) and beta weights (Bonferroni corrected $\alpha<.012$) were compared with RM-ANOVAs.
**Results:** FWD ($p=.035$) and BWD ($p<.001$) gait speed increased from pre to post. FWD was always faster than BWD ($p<.001$), and BWD increased more than FWD speed ($p=.004$). For the CBLM, M1, and PMC, MI-SD had lower activity compared to MI-FWD and MI-BWD ($p\leq.003$) at pre and post. There were no significant effects of group, time, nor interactions in any of the three regions of interest.
**Conclusions:** Despite similar responses to exercise for gait, neural activity did not change with exercise in FoG+ and FoG- in any of our selected regions of interest. Neural activity also did not differ between FoG+ and FoG-. The significant differences seen between the three imagined conditions may suggest that MI of static tasks such as standing do not recruit motor imagery networks in the same way as MI of dynamic tasks such as walking. Future analyses will examine more targeted cerebellar regions. This will provide an in depth look at neural activity within the cerebellum between static and dynamic MI tasks as well as in response to exercise.

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**Poster**

**480. Parkinson's Disease: Human Diagnostics and Molecular Genetics**

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**Topic:** C.03. Parkinson's Disease

**Support:** H2020-ICT-2014-644780

**Title:** The importance of using computers in populations with Parkinson's disease and spinal cord injury: A patients' and caregivers' perspective

**Authors: M. PLOTNIK**[1], Z. KATSAROUL[4], A. GOTLIEB[2], *A. GRINBERG[2], G. ZEILIG[2,3], R. KIZONY[5,2], S. BOSTANTJOPOULOU-KAMBOUROGLOU[6]
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**Abstract:** *Background:* Motor and non-motor symptoms of people with various types of disabilities affect their ability to use computers. Although they consider the use of computers as an important part of their everyday life, they face many operational difficulties. *Objective:* The purpose of the study was to evaluate the importance of computer use as perceived by patients with Parkinson's disease (PD) and Spinal Cord Injury (SCI), as well as by their caregivers. *Design/Methods:* Fifty PD individuals, (mean age: 59.1±8.05 years) and eighteen SCI patients (mean age: 45.4± 15.5 years) were included in the study. Patients' working habits with the computer were explored by means of a structured interview. Using the most pertinent data from this interview we designed a quantitative scale, focused on the contribution of the computer to various aspects of social life (CCSL). The questionnaire consisted of nine items, each scoring from 1 (not important) to 5 (very important). Then, twenty PD caregivers and fourteen SCI caregivers were interviewed using the same questionnaire as the patients, adapted for completion by proxy. *Statistical Analysis:* Reliability of the CCSL scale was assessed by means of Cronbach's alpha coefficient. Caregivers' scale scores were compared to those of their patients by means of the t test for independent samples. *Results:* A mean 13.6±9.1 and 20.5±9.1 years of computer experience, and a mean daily use of 3.9±2.4 and 5±3.4 hours, were reported for PD and SCI patients respectively. As for reliability analysis for the scale, Cronbach's alpha was 0.76 and 0.85 and item to total score correlations ranged from 0.224 to 0.649, and from 0.17 to 0.8 for PD and SCI CCSL scales, respectively. The mean (± SD) CCSL scale total score was 22.7±6.9 and 23.11±8.4 for PD and SCI patients, respectively. Single items that scored high for all were relevant to 'education' and 'work and employment'. PD patients also showed a high 'interpersonal interaction' score while SCI patients showed a high 'autonomy and self-determination' score. Caregivers' mean scores on the CCSL scale were similar to those of the patients (PD: *p=0.324*, *SCI: p=0.9*). *Conclusions:* Our preliminary results show that PD and SCI patients, and their caregivers, regard computer use as an important tool for a productive life. This information is important for the development of innovating technologies that may assist patients to overcome specific operational difficulties.

**Disclosures:** **M. Plotnik:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Horizon 2020. **Z. Katsaroul:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Horizon 2020. **A. Gotlieb:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Horizon 2020. **A. Grinberg:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Horizon 2020. **G. Zeilig:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Horizon 2020. **R. Kizony:** C. Other Research Support

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**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.01/W3

**Topic:** C.05. Neuromuscular Diseases

**Support:** Above and Beyond NB, LLC

**Title:** Intraspinal delivery of AAV2-NRTN for ALS - a dose-ranging study of safety, tolerability, biodistribution, and efficacy

**Authors: *S. K. GROSS**[1], B. SHIM[1], B. L. PETERSON[2], R. T. BARTUS[3], N. M. BOULIS[4], N. J. MARAGAKIS[5]
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**Abstract:** Neurotrophic factors as potential candidates for ALS therapeutics have previously been studied in the context of attempts to slow disease progression but for a variety of reasons, failed to show adequate efficacy in ALS patients. Previous studies in Parkinson's Disease (PD) models have shown promise with the use of recombinant adeno-associated virus serotype-2 (rAAV2)-neurturin (NRTN) [AAV2-NRTN] to provide neuroprotection and behavioral improvements in preclinical models which subsequently resulted in several clinical studies in patients with PD. Given that this neurotrophic compound has not been studied in the context of ALS, nor has this been combined with this focal gene therapy approach for the directed delivery of AAV2-NRTN into the cervical spinal cord, we conducted a study of AAV2-NRTN to assess the preclinical safety, tolerability, biodistribution, and efficacy of this compound in a preclinical ALS mouse model. $SOD1^{G93A}$ mice were tested in four large cohorts (n=22-25): AAV2-NRTN ($1.44x10^{11}$ vg/animal, "high dose"); AAV2-NRTN ($3.6x10^{10}$ vg/animal, "low dose"); formulation buffer (FB) vehicle control; naïve $SOD1^{G93A}$ control littermates. Behavioral grip strength testing was performed twice weekly until end stage of the disease. Immunohistochemical analyses were performed to look for variations in motor neuron (MN) numbers. Behavioral analyses showed a trend towards a more gradual weakening of the forelimb strength during disease course in both "high" and "low" dose animals when compared with both FB and naïve control animals. However, this did not translate to an extension in overall survival. There was a neuroprotective effect on the number of cervical MNs during the symptomatic phase of disease in both AAV2-NRTN animal groups, but by end stage, MN numbers in the cervical

region were not significantly different between the two dosing groups. This suggests that there is evidence for neuroprotection stemming from the targeting of neurturin to cervical MNs. As expected, this neuroprotection was found to be focal and did not spread beyond the immediate region of injection. Overall, there were no increases in morbidity, no changes in serum chemistries or blood counts and no cases of drug-related mortality. These data combined suggest that AAV2-NRTN is well tolerated in SOD1$^{G93A}$ mice, is able to be effectively expressed in cervical spinal MNs, has a focal biodistribution in the spinal cord, is not found outside of the target area, and shows neuroprotection and behavioral efficacy during the symptomatic phase of disease. Because there is a broad clinical experience for this compound, these data provide further evidence to support its study in ALS patients.

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**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.02/W4

**Topic:** C.05. Neuromuscular Diseases

**Support:** NIH/NINDS Grant R01NS091722

ALS Therapy Alliance Grant 2013-F-052

NSF Graduate Research Fellowship 2014165948

**Title:** Differential gene expression changes in vulnerable and non-vulnerable cortical pyramidal cell populations in ALS

**Authors: *M. V. MOYA**[1], R. D. KIM[1], C. E. SFERRAZZA[1], D. R. BLACKMAN[1], E. B. HOLZNER[1], S. B. PICKETT[1], N. HEINTZ[1,2], E. F. SCHMIDT[1]
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**Abstract:** Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that causes degeneration of motor neurons of the spinal cord and cortex. To fully understand the molecular mechanisms that establish selective vulnerability of these cells in ALS, we must determine how the disease progresses in these cells relative to other unaffected cell types. To accomplish this, our group has profiled gene expression changes in a vulnerable spinal-projecting population and a non-vulnerable pyramidal neuron population during disease progression in the cortex of the SOD1-G93A mouse model of familial ALS. By expressing a GFP-tagged ribosomal subunit specifically in each cell type, we isolated actively translated mRNAs from our cells of interest using Translating Ribosome Affinity Purification (TRAP). We compared cell type specific gene expression profiles between wild-type (WT) and SOD1-G93A mice to understand disease mechanisms by identifying molecular pathways that were up- or down-regulated in the two cell-types. Additionally, we compared the baseline gene expression profiles of the two cell types in WT mice to determine what makes the two cell-types inherently different. When these data were combined, we found that vulnerable spinal-projecting neurons show gene expression changes more typically associated with degenerating neurons, whereas non-vulnerable neurons display contrasting changes that could underlie mechanisms of resistance to SOD1-G93A. To determine if our mouse pyramidal neuron populations and the gene expression changes we observe in them are representative of human motor cortex and ALS, we identified markers for both neuronal types that are shared across mouse and human. Staining human tissue for these markers alongside proteins that are altered in SOD1-G93A mice allows us to establish the disease-relevance of our TRAP findings. We have established an approach for studying molecular changes that occur in vulnerable cells during disease by taking into account the underlying unique biological characteristics of those cells. This approach will allow us to understand how neurodegenerative diseases differentially affect specific neuron populations.

**Disclosures: M.V. Moya:** None. **R.D. Kim:** None. **C.E. Sferrazza:** None. **D.R. Blackman:** None. **E.B. Holzner:** None. **S.B. Pickett:** None. **N. Heintz:** None. **E.F. Schmidt:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.03/W5

**Topic:** C.05. Neuromuscular Diseases

**Support:** NHMRC

Nancy Frances Curry Scholarship

**Title:** Investigating the role of amyloid precursor like protein-2 in motor neuron disease

**Authors: *P. H. TRUONG**, G. D. CICCOTOSTO, P. J. CROUCH, R. CAPPAI
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**Abstract:** Motor neuron disease (MND), the most common form of which is amyotrophic lateral sclerosis, is a human neurodegenerative disorder characterized by progressive destruction of motor neurons in the central nervous system, muscle atrophy, paralysis and ultimately death. Although the majority of MND cases are of sporadic origin, 10-15% of MND cases are familial, commonly involving the genetic mutations in the Cu/Zn superoxide dismutase (SOD1) gene. Transgenic mouse models over-expressing the human mutant forms of SOD1 that recapitulate the pathological symptoms seen in MND patients are widely used to study MND. Despite intensive research to understand the molecular mechanisms of this disease, the cause and modulation of MND remains unclear. The Amyloid Precursor Protein (APP) is highly expressed in the brain and its expression is increased in the mutant SOD1 transgenic mouse model and in MND patients (Koistinen et al., 2006). Deletion of the APP gene in a transgenic SOD1 mouse model significantly slowed disease progression (Bryson et al., 2012). This suggests targeting APP protein expression could modulate disease outcomes in MND. APP is part of a gene family that includes the amyloid precursor-like protein 1 (APLP1) and amyloid precursor-like protein 2 (APLP2) genes. We have investigated the role of APLP2 in MND. Expression studies found a significant increase in the expression of APLP2 protein in brain of the $SOD1^{G37R}$ transgenic mouse model. To characterize how APLP2 gene expression can modulate disease outcomes in MND we crossed the $SOD1^{G37R}$ mouse with APLP2 knockout mouse model to generate $SOD1^{G37R}$ $APLP2^{+/-}$ and $SOD1^{G37R}$ $APLP2^{-/-}$ lines. Female $SOD1^{G37R}$ $APLP2^{+/-}$ mice exhibited a significantly reduced life span, an earlier onset and accelerated progression of disease, as compared to $SOD1^{G37R}$ $APLP2^{+/+}$ mice. By contrast, female $SOD1^{G37R}$ $APLP2^{-/-}$ mice had a significantly delayed disease progression and improved survival. Taken together, our results demonstrate there are gender related differences in the SOD1 mouse model, and this is affected by APLP2 expression. These data add further support for a modulatory role by the amyloid precursor protein family in MND, and identify the APP-family as an important target for further investigation into the cause and regulation of MND.

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**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

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**Program#/Poster#:** 481.04/W6

**Topic:** C.05. Neuromuscular Diseases

**Support:** NIH Grant NS099638

Foglia Family Foundation

Les Turner ALS Foundation

**Title:** Characterization of transgenic mice expressing ALS-associated CHCHD10-R15L

**Authors: *É. RYAN**[1], J. YAN[2], H.-X. DENG[2], T. SIDDIQUE[2]
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**Abstract:** Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 10 (CHCHD10) is a nuclear gene that encodes for a protein of unknown function that is enriched in mitochondria. We, and others, have identified mutations in CHCHD10 in a variety of degenerative diseases including, but not limited to, amyotrophic lateral sclerosis (ALS) and mitochondrial myopathy. Using the approach of whole exome sequencing, we identified an R15L missense mutation in CHCHD10 in individuals from a large, multi-generational familial ALS pedigree. The mutation was subsequently identified in four additional families. In an effort to better understand the pathogenic mechanism of this mutation, we engineered transgenic mouse models expressing either the wild type or mutant variants of human CHCHD10. Pathological, biochemical and behavioral characterization of these mouse lines has provided insight into the possible disease processes involved. Severe axonal pathology is apparent in a diverse range of neurons throughout the central nervous system in CHCHD10-R15L transgenic mice. The pathology is first evident around 60 days of age, yet the mice survive well beyond this. Although the CHCHD10-R15L transgenic mice have an abbreviated lifespan compared to controls, they perform comparably in motor behavior tasks up to the point of death. The cause of death is currently under investigation. Preliminary biochemical studies indicate that this mutation does not impair targeting of CHCHD10 protein to mitochondria or the efficiency of action of the electron transport chain. This novel mouse model supports the hypothesis that the R15L mutation impacts upon normal central nervous system functioning, as evident by the presence of axonal pathology. The mechanism by which the pathology manifests a behavioral deficit requires further investigation.

**Disclosures: É. Ryan:** None. **J. Yan:** None. **H. Deng:** None. **T. Siddique:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.05/W7

**Topic:** C.05. Neuromuscular Diseases

**Title:** Differential onset of behavioral and electrophysiological symptoms in the rNLS8 (hTDP-43ΔNLS) mouse model of TDP-43 pathology

**Authors: *P. T. LEACH**[1], M. SHPOKAYTE[2], A. SHEEHY[2], B. J. FARLEY[2], J. AMACKER[2], A. MCCAMPBELL[2], H. M. ARNOLD[2]
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**Abstract:** While specific mutations in TDP-43 (transactive response DNA binding protein 43 kDa, TARDBP) only account for 3-5% of ALS patients, TDP-43 pathology is present in the majority of ALS and FTD patients. Nearly all (97%) of Amyotrophic Lateral Sclerosis (ALS) patients exhibit ubiquinated cytoplasmic TDP-43 inclusions, despite this protein's typical nuclear localization, and nearly half (45%) of frontotemporal dementia (FTD) patients exhibit a similar TDP-43 pathology. Thus, a better understanding of this protein and its related pathology is critical to ALS research. The rNLS8 mouse model of TDP-43 pathology conditionally expresses a mutated version of hTDP-43 that lacks the nuclear location signal (ΔNLS), causing a reduction in endogenous mTDP-43 in the nucleus and instead forms cytoplasmic inclusions of hTDP-43 similar to those observed in human ALS patients. This mouse model has previously been shown to exhibit striking deficits in rotarod performance and an increased prevalence of hind-limb clasping, along with deficits in compound muscle action potential (CMAP) assessed in the gastrocnemius muscle. In the current study we confirmed these behavioral phenotypes and extended them to other behavioral and electrophysiological endpoints. Within five days of the initiation of the conditional expression of hTDP-43ΔNLS, rotarod deficits were evident, while a hind limb clasping response did not emerge until much later, about two weeks after onset of the disease model. We observed CMAP deficits in the tibialis anterior muscle, which supports the previous findings in the gastrocnemius muscle, but this deficit did not appear until three weeks after the onset of the disease model. Despite the dramatically decreased rotarod performance, these mice were observed to be hyperactive in an open field starting around 2 weeks, and remained so for up to 5 weeks, following the onset of abnormal gene expression. To our knowledge, this is the first time that hyperactivity has been reported in the rNLS8 TDP-43 mouse model of ALS, and it seems to be in contrast to the loss of coordination observed in the rotarod test. This finding is reminiscent of the long-standing debate in the ALS research field over whether physical activity is positively correlated with an increase in the risk of developing ALS symptoms. More research is needed to demonstrate if there is a causal relationship to this effect.

**Disclosures:** **P.T. Leach:** A. Employment/Salary (full or part-time):; Biogen. **M. Shpokayte:** A. Employment/Salary (full or part-time):; Biogen. **A. Sheehy:** A. Employment/Salary (full or part-time):; Biogen. **B.J. Farley:** A. Employment/Salary (full or part-time):; Biogen. **J. Amacker:** A. Employment/Salary (full or part-time):; Biogen. **A. McCampbell:** A. Employment/Salary (full or part-time):; Biogen. **H.M. Arnold:** A. Employment/Salary (full or part-time):; Biogen.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.06/W8

**Topic:** C.05. Neuromuscular Diseases

**Support:** Sims Family Fund

**Title:** Spinal muscular atrophy with respiratory distress: New CRISPR-based models and the search for a genetic modifier of disease

**Authors: *P. MARTIN**, A. H. HICKS, J. E. STAUFFER, D. G. SCHROEDER, G. A. COX
Cox Lab., Jackson Lab., Bar Harbor, ME

**Abstract:** Spinal Muscular Atrophy with Respiratory Distress (SMARD1) is a lethal autosomal recessive infantile disease, characterized by the loss of motor neurons leading to muscular atrophy, weakness of the truck and limbs and diaphragmatic weakness. Mutations in a DNA/RNA 5' to 3' helicase, *Ighmbp2*, have been shown to cause SMARD1 and more recently Charcot-Marie-Tooth disease (CMT), a less severe disease characterized by progressive motor and sensory polyneuropathy. Currently there is only one mouse model to study mutations in *Ighmbp2*, the neuromuscular degeneration ($nmd^{2J}$) mouse, which carries a hypomorphic splicing mutation which reduces wild-type protein expression. A genetic modifier region from CAST/EiJ ($Mnm^{C}$) has been mapped to Chromosome 13 and found to suppress the disease. This region contains one protein-coding gene *Zfp322a* as well as a number of tRNAs. We have created new *Ighmbp2* mutant alleles, through the use of CRISPR-CAS9 technologies, that display significant phenotypic variation relative to the $nmd^{2J}$ allele. Characterization of these models has identified two very severe models that fail to survive more than a day or two after birth, one early-onset model that typically lives 2-3 weeks and one mild disease model that may more closely resemble CMT. Not only do these mice have a reduction in lifespan, but they also have a significant reduction in motor neurons as well as increase muscular atrophy. Our characterization of these new models suggest that they recapitulate the phenotypic variation seen in the human patients and can aid in understanding the endogenous functions of *Ighmbp2*. We also aim to identify what specifically in the CAST-derived congenic modifier region ($Mnm^{C}$) is driving suppression by utilizing a CRISPR strategy to knock out each gene in turn to determine which are responsible for modulating disease severity. Our preliminary evidence suggests that *Zfp322a* null mice are viable as homozygotes and we are crossing them with our $nmd^{2J}$ mice to determine if the modifier region still suppresses disease. By identifying the modifier, we may indicate which cellular pathways *Ighmbp2* works in. The creation and characterization of these novel alleles and interrogation of the $Mnm^{C}$ region, broadens our knowledge of the function of *Ighmbp2* in the motor neurons and may allow us to identify potential therapeutic strategies.

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**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.07/W9

**Topic:** C.05. Neuromuscular Diseases

**Support:** ALSA

University of Florida

McKnight Brain Institute (UF)

**Title:** Similar muscle pathology but disparate phenotypes in transgenic mice expressing WT and F115C mutant Matrin 3

**Authors: *J. M. LEWIS**[1], C. MOLONEY[2], S. RAYAPROLU[4], J. HOWARD[2], S. FROMHOLT[2], M. SWANSON[2], H. BROWN[2], L. NOTTERPEK[5], D. R. BORCHELT[3]
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**Abstract:** Mutations in the nuclear matrix protein Matrin 3 are associated with amyotrophic lateral sclerosis (ALS) and distal myopathy with vocal cord and pharyngeal weakness. Previously, we generated and characterized transgenic mice expressing wild-type human Matrin 3 under the mouse prion promoter (PrP-$^{WT}$MATR3). These mice develop a phenotype of hindlimb paresis or paralysis with hindlimb and forelimb muscle atrophy. Pathological analysis of the gastrocnemius and bicep of phenotypic mice showed a striking presence of vacuoles, nuclear chains, rounded fibers, and an increase in Matrin 3 immunoreactive internal nuclei in the fibers. Upon further analysis, we found that both distal and proximal muscles of the hindlimb (soleus, tibialis anterior, and quadriceps) and forelimb muscles (triceps and extensor carpi radialis) show similar pathology including vacuoles and rounded fibers. Although there appeared to be no increase in Matrin 3 protein levels in the spinal cord of the PrP-$^{WT}$MATR3 mice, spinal cords of phenotypic mice showed increased gliosis and individual neurons appeared to have higher MATR3 levels and/or with cytoplasmic immunostaining of Matrin 3. We have now generated equivalent PrP-MATR3 mice that express the F115C mutant Matrin associated with ALS (PrP-$^{F115C}$MATR3). By two months of age, most PrP-$^{F115C}$MATR3 mice develop similar muscle pathology to the PrP-$^{WT}$MATR3 mice, including the robust presence of vacuoles; however, only a few PrP-$^{F115C}$MATR3 mice with this pathology develop motor dysfunction. These data indicate that the muscular pathology, per se, is not directly causative for the motor

phenotype and suggests that defects in the spinal cord or neuromuscular junction are more likely the source of the motor phenotype. These potential deficits are currently being assessed in both PrP-$^{WT}$MATR3 and mutant PrP-$^{F115C}$MATR3 transgenic mice. Understanding the origin of the phenotype disparity across these mouse lines may provide insight on disease mechanism and/or the normal role of Matrin 3.

**Disclosures:** **J.M. Lewis:** A. Employment/Salary (full or part-time):; University of Florida. **C. Moloney:** None. **S. Rayaprolu:** None. **J. Howard:** None. **S. Fromholt:** None. **M. Swanson:** None. **H. Brown:** None. **L. Notterpek:** None. **D.R. Borchelt:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.08/W10

**Topic:** C.05. Neuromuscular Diseases

**Support:** MDA grant

**Title:** TRPV4-mediated motor impairment, aberrant calcium signaling, and disrupted mitochondrial axonal transport in a *Drosophila* model of CMT2C

**Authors: *B. WOOLUMS**[1], M. TABUCHI[2], H. SUNG[2], J. M. SULLIVAN[2], B. MCCRAY[2], C. MAMAH[2], M. YANG[2], M. N. WU[2], C. J. SUMNER[2], T. E. LLOYD[2]
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**Abstract:** Dominant missense mutations in the gene encoding the cation channel transient receptor *vanilloid*, family member 4 (TRPV4) cause inherited neuropathies including Charcot-Marie-Tooth disease 2C (CMT2C). *in vitro*, mutations in TRPV4 that cause CMT2C cause a gain of TRPV4 channel function and increased intracellular calcium which subsequently leads to cellular toxicity. However, the mechanisms by which CMT2C mutations in TRPV4 lead to neuronal dysfunction *in vivo* remain poorly understood. We generated transgenic *Drosophila* that express either wild-type or a CMT2C causing TRPV4 mutant (TRPV4$^{R269C}$) to assess the effect of TRPV4$^{R269C}$ on neuron function *in vivo.* Selective expression of TRPV4$^{R269C}$ in *Drosophila* CCAP neurons ($N_{CCAP}$) results in a failure of *Drosophila* wing expansion that is blocked by genetically inactivating the channel pore, demonstrating the requirement of channel function in mediating this phenotype. Perforated patch clamp analysis of $N_{CCAP}$ reveals that TRPV4$^{R269C}$ causes a calcium-dependent increase in $N_{CCAP}$ neuronal excitability. This hyperexcitability is restored to control levels by application of a TRPV4 selective antagonist. High level expression of TRPV4$^{R269C}$ causes synaptic and dendritic degeneration, both of which are rescued genetically by inactivating the channel pore or pharmacologically by feeding larvae a TRPV4 selective antagonist. We conducted a genetic screen in $N_{CCAP}$ and found that CaMKII knockdown potently

suppresses the TRPV4$^{R269C}$ mediated wing expansion phenotype and selectively rescues degeneration of synapses but not dendrites. We also find that TRPV4$^{R269C}$, but not controls, disrupts mitochondrial transport in axons by increasing the number of stationary mitochondria. We have also found that induction of TRPV4$^{R269C}$ expression after eclosion causes progressive motor impairment, suggesting TRPV4$^{R269C}$ can cause a progressive neuropathy that is independent of any developmental processes TRPV4$^{R269C}$ may disrupt. Our data demonstrate that TRPV4$^{R269C}$ causes a progressive neuropathy in our *Drosophila* model of CMT2C likely through elevated neuronal intracellular calcium which disrupts mitochondrial transport and mediates neurodegeneration through compartment-specific calcium-mediated signaling pathways. These findings support further investigation of TRPV4 antagonists as potential therapeutics for the treatment of CMT2C.

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**Poster**

**481. Motor Neuron Disease: Animal Models II**

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ALS Association

Packard Center

**Title:** Autophagolysosomal disruption in *Drosophila* models of ALS/FTD caused by C9orf72 mutations

**Authors: *K. CUNNINGHAM**[1], K. ZHANG[1], M. SENTURK[2], H. SUNG[1], K. RUAN[1], Z. ZUO[2], H. J. BELLEN[2], T. E. LLOYD[1]
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**Abstract:** A GGGGCC hexanucleotide repeat expansion (G4C2 HRE) in an intron of the C9orf72 gene has been identified as the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). One of the pathological hallmarks of C9-ALS is the presence of cytoplasmic protein aggregates colocalized with the autophagy receptor

p62/SQSTM1. Interestingly, mutations in p62/SQSTM1 are also a rare genetic cause of ALS through an unclear mechanism. In a Drosophila model of C9-ALS expressing $(G4C2)_{30}$, we have found that p62 is upregulated and forms large aggregates in motor neurons. p62 plays a key role in autophagy by binding ubiquitinated proteins and delivering them to the autophagosome for degradation via the lysosome. Surprisingly, we find that knockdown of p62 rescues degeneration in the fly eye and in motor neurons. Immunofluorescence and western blot analysis of autophagy and lysosome markers demonstrates an expansion of lysosomes and a decrease of delivery to and digestion of autophagic cargo in the lysosome. Using electron microscopy of the *Drosophila* eye we observe a remarkable accumulation of expanded multilamellar bodies and autolysosomes that precedes neurodegeneration. Because we have also found that nucleocytoplasmic transport is disrupted in $(G4C2)_{30}$ flies, we are investigating the relationship between defects in protein degradation and nucleocytoplasmic transport disruption. We propose that C9orf72-HRE expression causes dysregulation of protein folding and degradation leading to cytotoxic protein aggregation, and that this is rescued by aggregate clearance through genetic and pharmacological upregulation of chaperones, autophagy, and the ubiquitin-proteasome system. This study suggests that drugs targeting proteostasis pathways may have therapeutic potential for C9orf72-mediated ALS and FTD.

**Disclosures: K. Cunningham:** None. **K. Zhang:** None. **M. Senturk:** None. **H. Sung:** None. **K. Ruan:** None. **Z. Zuo:** None. **H.J. Bellen:** None. **T.E. Lloyd:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.10/W12

**Topic:** C.05. Neuromuscular Diseases

**Support:** NS078504

Foglia Family Foundation

Les Turner ALS Foundation

**Title:** Molecular desection of ALS pathogenesis of ubiquilinopathy using CRISPR/Cas9

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**Abstract:** Ubiquilin2 belongs to ubiquitin like protein family and regulates protein degradation through ubiquitin proteasome system (UPS). Mutations impair protein degradation and lead to abnormal protein aggregations and neuronal loses. The $UBQLN^{P497H}$ transgenic mice developed

neuronal pathology, characterized by ubiquilin2/ubiquitin/P62 positive inclusions in the brain. Mutant ubiquilin2 impairs proteasome function by a gain of function mechanism yet to be determined. Methods: Use CRISPR/Cas9 system to introduce mouse P511H mutation which is equivalent to human P497H mutation into mouse genome. Mice tissues were collected undergo pathological analysis. Results: We established three different mice strains: ubiquilin2 KI mouse introduced P511H/human P497H mutant; the in-frame deletion of mouse I512-V552/human I498-V538 which removed PXX domain ranging from P491-G526; and 1bp deletion resulted a truncated protein I498Mfs*7 with no PXX and UBA domain. The founders were 11 months old with no obvious motor phenotypes. Three $100^{\pm}$-day old progenies from ubiquilin2 KI mice tissues were underwent pathological analysis. The hippocampus region displayed small ubiquilin2 positive aggregates with similar pattern as the reported ubiquilin2 transgenic mice, but were much less extensive. Other regions of brain showed similar staining pattern. The ubiquilin2 positive aggregates were also positive for P62, but not ubiquitin. Antibodies against 26s proteasome subunits, 19s regulatory particle (ADRM1) and 20s enzymatic core particle (PSMA3), were positive. The KI transgenic mice expressed mouse ubiquilin2 protein at comparable level as the non-transgenic mouse detected by Western blot. Discussion/conclusions: The milder pathological changes in the KI mouse models may be caused by lower protein level associated with CRISPR/Cas9 system, but may better mimic human condition than the old system. Further studies with the other two mice strains with deletion of PXX and UBA domains shall provide more insight into the mechanism of neuropathy. Furthermore introduce a UBL point mutation to abolish proteasome binding domain will narrow the proteasome dysfunction into precise functional domain.

**Disclosures:** **Y. Shi:** None. **H. Deng:** None. **H. zhai:** None. **E. liu:** None. **T. siddique:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

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**Topic:** C.05. Neuromuscular Diseases

**Support:** University Medical Center Giessen and Marburg (UKGM, Germany)

P. E. Kempkes Foundation (University of Marburg, Germany)

German Society for the Muscular Diseased (DGM, Freiburg, Germany)

**Title:** A new pathology hallmark of amyotrophic lateral sclerosis: Inflammation-independent dendropathy in excitatory neuronal subsets of the olfactory bulb and retina of SOD1-G93A mutant mice

**Authors: *B. SCHUETZ**[1], E. WEIHE[2], C. RINGER[3,4]
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**Abstract:** Non-motor neuron-related pathology is a feature of amyotrophic lateral sclerosis (ALS), both in patients and in animal models. There is emerging evidence that sensory systems, i.e. olfaction and vision, are affected in humans. Here we asked whether such sensory neuropathology is recapitulated in the superoxide dismutase 1 (SOD1-G93A) mouse model of ALS. Human SOD1-related vacuolization as pathology marker was assessed in olfaction and vision pathways from pre-symptomatic and symptomatic disease stages using immunohistochemistry, and compared to wild type. In both, the olfactory bulb and retina, vacuolization started around postnatal day 60, and vacuole sizes increased until disease end-stage. Notably, vacuolization was largely restricted to the external plexiform layer of the olfactory bulb and to the inner plexiform layer of the retina. In both layers, hSOD1-immunoreactive vacuoles localized to dendrites of excitatory neurons. Downstream olfaction and vision pathway fiber tracts and relay stations did not display obvious vacuolization. Finally, on a morphological level, there was no evidence for an activation of astrocytes and microglia in the two affected areas. Thus, we identified a new pathology hallmark in SOD1-G93A ALS mice, i.e. a glutamatergic sensory neuron dendropathy restricted to olfactory bulb mitral cells and retinal ganglionic cells.

**Disclosures: B. Schuetz:** None. **E. Weihe:** None. **C. Ringer:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

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Interuniversity Attraction Poles program [P7/16]

**Title:** C9orf72 zebrafish model relates RNA toxicity to autophagy and stress granules

**Authors: B. SWINNEN**[1], A. BENTO-ABREU[2], T. GENDRON[3], S. BOEYNAEMS[2], E. BOGAERT[2], R. NUYTS[2], M. TIMMERS[2], W. SCHEVENEELS[2], J. WANG[4], S. MIZIELINSKA[5], A. ISAACS[5], L. PETRUCELLI[3], *P. VAN DAMME[6], L. VAN DEN BOSCH[2], W. ROBBERECHT[1]
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**Abstract:** A hexanucleotide repeat expansion in the C9orf72 gene has been shown to be the most frequent cause of ALS. Neurotoxicity is believed to be mediated by either (or a combination of) RNA toxicity, DPR toxicity or loss of function of the C9orf72 protein. The aim of this study was to develop an *in vivo* zebrafish model to investigate these mechanisms, and more specifically to disentangle RNA toxicity and DPR toxicity. Injection of repeat RNA as well as some DPR constructs (in particular GR and PR) into zebrafish oocytes induced a motor neuronal phenotype at 30 hours post fertilization. Using dot blot, Western blot and ELISA, generation of significant amounts of DPRs in fish injected with repeat RNA was excluded. Moreover, synergistic toxicity between low (not toxic) levels of the different DPRs was excluded. Additionally, interrupted repeat RNA constructs which are unable to generate DPRs were found to be neurotoxic as well. Hence, toxicity of repeat RNA seems to be mediated by direct RNA toxicity, independent of DPR toxicity. To investigate the mechanism of this RNA toxicity we tested whether overexpression of three RNA binding proteins (Pur-alpha, HNRNPA1 and HNRNPH1), that have been shown to be able to bind repeat RNA, could alleviate this toxicity. Interestingly, Pur-alpha indeed prevented RNA toxicity, whereas it had no effect on DPR toxicity. This protective effect relied on both its glycine-rich and PUR2 domain. The PUR2 domain was found to be responsible for induction of p62 levels. Interestingly, overexpression of p62 equally protected against RNA toxicity. Deletion of the glycine-rich domain, being a low complexity domain, was found to perturb the regulatory effect of Pur-alpha on stress granules. In conclusion, we show that neurotoxicity of C9orf72 repeat expansion is mediated, at least in part, by direct RNA toxicity, independent of DPR toxicity. We show that the RNA binding protein Pur-alpha as well as the autophagy related protein p62 prevent this RNA toxicity, relating RNA toxicity to perturbations in autophagy and stress granules.

**Disclosures:** **B. Swinnen:** None. **A. Bento-Abreu:** None. **T. Gendron:** None. **S. Boeynaems:** None. **E. Bogaert:** None. **R. Nuyts:** None. **M. Timmers:** None. **W. Scheveneels:** None. **J. Wang:** None. **S. Mizielinska:** None. **A. Isaacs:** None. **L. Petrucelli:** None. **P. Van Damme:** None. **L. Van Den Bosch:** None. **W. Robberecht:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.13/W15

**Topic:** C.05. Neuromuscular Diseases

**Support:** NIH Grant R01-NS094239

**Title:** *In vivo* imaging of axonal transport in a *Drosophila* model of c9-als

**Authors: *H. SUNG**, T. LLOYD
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**Abstract:** Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by preferential death of motor neurons in the brain and spinal cord. Although the majority of ALS cases are sporadic, a $G_4C_2$ hexanucleotide repeat expansion (HRE) in *C9orf72* is the most common inherited cause of ALS (C9-ALS). Since ALS displays selective vulnerability of motor neurons with early evidence of distal axonopathy, we hypothesize that disruption of axonal transport by $G_4C_2$ HRE may be a critical factor in C9-ALS motor neuronal degeneration. Here, we investigated the axonal transport of different organelles, including mitochondria, dense core vesicles (DCVs) and autophagic vacuoles (AVs) in *Drosophila* expressing 30 $G_4C_2$ repeats. For *in vivo* imaging, we monitored motor axons from intact 3$^{rd}$ instar larvae, and obtained time-lapse images by using laser scanning confocal microscopy within 10 minutes of larval dissection. We found that expression of the $G_4C_2$ HRE reduces the number of axonal AVs and retrograde movements of autophagosomes, while the movements of DCVs in motor axons were not altered. These results suggest that organelle-specific disruption of axonal transport of autophagosomes may occur in C9-ALS, and further implicate protein quality control disruption, resulting in protein aggregate formation and/or autolysosomal dysfunction, in this disease.

**Disclosures: H. Sung:** None. **T. Lloyd:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

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**Program#/Poster#:** 481.14/W16

**Topic:** C.05. Neuromuscular Diseases

**Support:** WaterWheel Foundation

**Title:** Gene-environment interactions in amyotrophic lateral sclerosis

**Authors: *R. SHER**[1], S. KWOK[2], E. LOVEJOY[2], T. LAVIN[2], S. POWERS[3], M. KRUGER[2]
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**Abstract: Background:** The scientific consensus is that gene-environment interactions are key for the development and progression of ALS, but how either toxicants or genes lead to a disease mechanism is currently unknown. A suite of environmental neurotoxicants has been associated with ALS, with evidence indicating that early developmental exposures to neurotoxins can have consequences for neurotoxicity later in life. Early defects in neural circuitry have also been found to be associated with late-onset neurological disorders, including both cognitive and degenerative diseases. By determining cellular pathways involved in modifying neurological defects we hope to gain a better understanding of the root causes of this disorder.
**Objectives:** Our research aims to study the intersection of genetics and environmental neurotoxins on both developmental motor neuron defects and on adult-onset disease in a zebrafish model of ALS.
**Methods:** We have determined the impact of embryonic exposure to environmentally relevant doses (0-25µg/L) of the ALS-associated cyanobacterial neurotoxin Beta-methylamino-L-alanine on neurodevelopmental defects in mutant SOD1-ALS zebrafish, and on consequences for adult motor function.
**Results:** (1) Tg-SOD1-G93R zebrafish exhibit significantly shorter 30hpf motor neurons at medium doses (10µg/L BMAA) but Tg-SOD1-WT overexpressing embryos are not impacted at all. (2) Five-month old Tg-SOD1-G93R fish (embryonically exposed to BMAA) show decreased ability to swim against water current, with increasing embryonic BMAA dose having a negative impact on swimming ability. In contrast, Tg-SOD1-WT fish exhibit an increased swimming ability with increasing BMAA dose. (3) Five month Tg-SOD1-G93R fish also show increasing fatigue when repeatedly challenged in the water current, while Tg-SOD1-WT fish do not exhibit any change in swimming over repeated challenges.
**Discussion:** Our results indicate that genetic and environmental insults combine to facilitate neurological dysfunction in ALS, and that overexpression of wt-SOD1 may have protective effects against neurotoxin damage. The defects seen in early neurodevelopment are mirrored at 5 months of age in the ability of fish to swim against a current and to fatigue with repeated swimming challenges. Establishing these links between exposure and adult motor neuron disease increases the power of the zebrafish model for toxicological and drug screens.

**Disclosures:** **R. Sher:** A. Employment/Salary (full or part-time):; Stony Brook University. **S. Kwok:** None. **E. Lovejoy:** None. **T. Lavin:** None. **S. Powers:** None. **M. Kruger:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

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**Topic:** C.05. Neuromuscular Diseases

**Support:** NIH-R21- NS085750-01

Les Turner ALS association

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**Title:** Transcriptome analysis of corticospinal motor neurons that lack Alsin function

**Authors: *M. GAUTAM**[1], L. A. LABOISSONNIERE[3], M. KANDPAL[2], M. C. SCHULTZ[1], Y. BI[2], J. M. TRIMARCHI[3], R. V. DAVULURI[2], P. H. ÖZDINLER[1]
[1]Neurol., [2]Preventive Medicine-Health and Biomed. Informatics, Northwestern Univ., Chicago, IL; [3]Dept. of Genetics, Develop. and Cell Biol., Iowa State Univ., Ames, IA

**Abstract:** Corticospinal motor neurons (CSMN) are unique in their ability to collect and integrate signals from different regions of the cerebral cortex and relay that information to the spinal cord targets. Thus, they play an important role for the initiation and modulation of voluntary movement. CSMN degeneration has been central in hereditary spastic paraplegia (HSP), primary lateral sclerosis (PLS) and in amyotrophic lateral sclerosis (ALS). Mutations in various genes result in motor neuron vulnerability, progressive degeneration, and dysfunction of motor neuron circuitry. Alsin is a member of the small GTPases gene family that are involved in cytoskeleton maintenance and vesicle trafficking inside the cell, among other important functions. Mutations in the Alsin gene have been shown to manifest into early onset ALS, in which upper motor neurons are primarily affected. Our study reveals the molecular and genetic mechanisms that are
involved in the very early stages of neuronal dysfunction in the absence of Alsin. We previously generated and characterized UCHL1-eGFP mice, in which CSMN are genetically labelled with eGFP expression that is stable and long lasting. This reporter line distinguishes CSMN from other neurons in the motor cortex and allows their specific and precise investigation. The UCHL1-eGFP mice were crossbred with $Alsin^{KO}$ mice to generate $Alsin^{KO}$-UeGFP mice, allowing purification of CSMN that lack alsin function via FACS-mediated approaches. We performed RNA-Seq analysis on pure populations of CSMN isolated from $Alsin^{KO}$-UeGFP and used CSMN from $Alsin^{WT}$-UeGFP mice as the healthy control. Our ongoing study reveals key cellular events that are affected even at very early stages of the disease. Genes involved in fatty acid metabolism, immune response, and mitochondrial functions were found differentially regulated. We also identified key genes that are alternatively spliced in the absence of Alsin.

Upon completion, this study will uncover important molecular clues about why upper motor neurons degenerate in the absence of alsin function.

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**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 481.16/W18

**Topic:** C.05. Neuromuscular Diseases

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**Title:** Defects in a dynamic tubular lysosomal network drive age-related degeneration of neurons and muscle

**Authors: *A. E. JOHNSON**[1], B. O. ORR[1], A. TONG[1], G. W. DAVIS[1,2]
[1]Biochem. and Biophysics, UCSF, San Francisco, CA; [2]Kavli Inst. for Fundamental Neurosci., San Francisco, CA

**Abstract:** Age-related degenerative diseases including Amyotrophic Lateral Sclerosis (ALS), Alzheimer's disease (AD) and Parkinson's disease (PD), are becoming more prevalent as the average life expectancy continues to rise. The current lack of disease-modifying treatments to alter the course of degenerative diseases reflects our lack of knowledge about the molecular basis of the disease pathology. An early hallmark common to most degenerative diseases is an accumulation of protein aggregates and damaged organelles, implying underlying defects in proteostasis. The predominant cellular degradation sites for clearing damaged proteins and organelles are lysosomes and lysosome dysfunction has been linked to a broad spectrum of degenerative diseases. In recent years, it has become apparent that lysosomes are not rigid organelles. Instead, lysosomes have been observed to adopt highly plastic states, altering their shape, size and molecular components to accommodate changing intracellular and extracellular environments. We previously demonstrated that lysosomes can form extended, highly dynamic, tubular networks in diverse cell types including muscles and glia. Additionally, we found that the integrity and maintenance of tubular lysosomes requires the activity of Valosin Containing Protein (VCP/p97), a AAA+ ATPase that when mutated causes muscle, bone and neuronal degenerative diseases (Johnson et al., *eLife* 2015). These data suggest that the integrity of this

unique class of tubular lysosomes may be directly relevant to the cause of VCP-related degenerative diseases. However, VCP has many diverse functions within the cell, so to elucidate the specific function of VCP at the tubular lysosomal network, we developed genetic tools in *Drosophila* to specifically disrupt VCP at tubular lysosomes, without disrupting its other cellular functions. Using these genetic models, we find that loss of VCP function at tubular lysosomes correlates with defects in tubular lysosome fusion, autophagy-dependent clearance of protein aggregates and subsequently leads to progressive muscle and neuronal degeneration. Mechanistically, we have identified a small VCP interacting protein (SVIP) that directly recruits VCP to tubular lysosomes and a specific disease-causing mutation in VCP that impedes VCP-SVIP interaction. Collectively, our data suggest that defects in tubular lysosome function are an underlying molecular cause for age-related degenerative diseases caused by VCP mutations.

**Disclosures:** **A.E. Johnson:** None. **B.O. Orr:** None. **A. Tong:** None. **G.W. Davis:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

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**Topic:** C.05. Neuromuscular Diseases

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**Title:** Calpain-dependent degradation of nucleoporins contributes to motor neuron death in a mouse model of chronic excitotoxicity

**Authors: *K. SUGIYAMA**, T. AIDA, K. TANAKA
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**Abstract:** Glutamate-mediated excitotoxicity induces neuronal death by altering various intracellular signaling pathways and has been considered as a final common pathway of neuronal death in several neurological disorders, such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis. Interestingly, nucleocytoplasmic transport defect has been recently reported in several neurological disorders. However, its contribution to excitotoxic cell death and the molecular mechanisms linking excitotoxicity to nucleocytoplasmic transport dysfunction remain still unknown. To investigate the mechanisms of excitotoxic neuronal death *in vivo*, we developed a novel animal model of chronic excitotoxicity by conditionally deleting astroglial glutamate transporters, which play pivotal role in preventing neurons from

excitotoxicity by reuptake of extracellular glutamate, GLT1 and GLAST in the spinal cords of mice (GLAST$^{+/-}$/GLT1-cKO). GLAST$^{+/-}$/GLT1-cKO mice displayed severe hindlimb paralysis and motor neuron death in lumbar ventral horn, and these abnormalities were reversed by AMPA receptor antagonist perampanel, but not NMDA receptor antagonist memantine. GLAST$^{+/-}$/GLT1-cKO mice also exhibited nuclear irregularity and calpain-mediated degradation of NPCs, which is responsible for nucleocytoplasmic transport. The nuclear export inhibitor KPT-350 prevented motor neuron death at an early stage, whereas long-term treatment of the AMPA receptor antagonist perampanel and the calpain inhibitor SNJ-1945 has continued beneficial effects in these abnormalities. Thus, exacerbated nuclear export due to NPC degradation is involved in excitotoxic neuronal death at an early stage, and preventing NPC degradation by calpain inhibitor and/or AMPA receptor antagonist has robust protective effects on motor neurons. Our results suggest the maintenance of NPC function serves as a novel therapeutic strategy in many neurological disorders.

**Disclosures:** **K. Sugiyama:** None. **T. Aida:** None. **K. Tanaka:** None.

**Poster**

**481. Motor Neuron Disease: Animal Models II**

**Location:** Halls A-C

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**Program#/Poster#:** 481.18/W20

**Topic:** C.05. Neuromuscular Diseases

**Support:** NIH Grant 1 R15 GM119099-01

**Title:** Exploring neuron-specific RNA-protein regulatory networks in the tunicate Ciona robusta

**Authors:** ***M. RUGGIU**[1], M. F. HOSSAIN[1], A. STOLFI[2], L. CHRISTIAEN[2]
[1]Dept. of Biol. Sci., St. John's Univ., Jamaica, NY; [2]Biol., New York Univ., New York, NY

**Abstract:** Tunicates (or sea squirts) are the closest living relatives to vertebrates. Adult sea squirts are simple, sessile, filter-feeding animals, but their free-swimming tadpole larvae are composed of only ~2600 cells, and display a simplified body plan that is chordate in mode of development. The dorsally located larval central nervous system of the sea squirt *Ciona robusta* comprises only 177 neurons distributed rostrocaudally in a brain vesicle, a motor ganglion and a nerve cord. Due to its small size, cellular simplicity, rapid development, and streamlined, compact genome that has not undergone the duplications seen in vertebrates, *Ciona* is particularly amenable to molecular perturbation and imaging, and its connectome is only the second one to be completely mapped after that of the nematode *C. elegans*. We present data here showing that *Ciona* can be a powerful model organism to study RNA-regulatory networks that are critical for neuron biology. NOVA1 and NOVA2 are splicing regulators specifically expressed in neurons and targeted in an autoimmune paraneoplastic motor neuron disorder.

Molecular analysis of NOVA function in vertebrates is complicated by the presence of two NOVA genes. A known NOVA target is a neuron-specific splice form of the ubiquitously expressed secreted proteoglycan AGRIN termed $Z^+$ AGRIN. This neuron-specific splice form of AGRIN is critical for the formation, development, and maintenance of the neuromuscular junction (NMJ), as it promotes clustering of the acetylcholine receptors (AChRs) by interacting with the transmembrane receptor LRP4 in muscle cells. Interestingly, AGRIN mutations lead to congenital myasthenic syndrome, and deterioration of the NMJ is at the center of Amyotrophic Lateral Sclerosis. We cloned the *Ciona* ortholog of NOVA, which is present as a single copy gene in tunicates, and that of AGRIN, and characterized their function and expression pattern during larval development. We discovered that, as in vertebrates, Agrin also undergoes alternative splicing to generate the $Z^+$ isoforms in *Ciona*, indicating that the Nova-Agrin-Lrp pathway for AChR clustering is shared between tunicates and mammals. However, we present evidence for coevolution between Nova proteins and the *cis*-regulatory sequences embedded in Agrin introns that promote Nova-dependent alternative splicing, revealing "developmental system drift" of an otherwise highly conserved RNA regulatory switch.

**Disclosures:** **M. Ruggiu:** None. **M.F. Hossain:** None. **A. Stolfi:** None. **L. Christiaen:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.01/W21

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH grant NS084817

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**Title:** Reduced $Ca^{2+}$ influx through voltage-gated $Ca^{2+}$ channels is associated with hyper-activity of striatal medium spiny neurons in the HIV brain

**Authors: *C. KHODR**, L. CHEN, L. AL-HARTHI, X.-T. HU
Dept. of Immunity and Emerging Pathogens, Rush Univ. Med. Ctr., Chicago, IL

**Abstract:** Up to 50% of $HIV^+$ patients have deficits in attention, working memory and psychomotor behavior, termed HIV-Associated Neurocognitive Disorders (HAND). Cortico-striatal pathways regulate these HIV-affected behaviors. We have reported that HIV increases the excitability of pyramidal neurons in the medial prefrontal cortex (mPFC), using HIV-1 transgenic (Tg) rats. Glutamatergic projections from these mPFC neurons innervate the caudate-putamen (CPu), where GABAergic medium spiny neurons (MSNs) are the prevalent neuronal

population. Here, we examined the impact of HIV on $Ca^{2+}$ influx and functional activity of MSNs in the CPu from 12 month-old HIV-1 Tg rats. The majority of neurons exhibited spike responses at rheobase currents ≤300pA (63.6% in non-Tg and 65.0% in HIV-1 Tg rats). In these neurons, we found increased neuronal firing in HIV-1 Tg rats compared to non-Tg rats. To determine if $Ca^{2+}$ influx through voltage-gated $Ca^{2+}$ channels (VGCCs) is involved in the increased firing in striatal MSNs (as we previously demonstrated in mPFC neurons of adolescent HIV-1 Tg rats), $Na^{+}$ channels, $K^{+}$ channels, and excitatory/inhibitory inputs were blocked in this study. We found that neuronal $Ca^{2+}$ influx was significantly reduced in HIV-1 Tg rats compared to non-Tg rats, which was accompanied by increased protein levels of a less functional, cleaved form of the $Ca_v1.2$ L-type VGCC in the CPu of HIV-1 Tg rats. The levels of full length $Ca_v1.2$ and $Ca_v1.3$ L-type VGCC protein were unaltered. These results indicate that VGCCs are not functionally involved in the increased MSN spiking in the HIV-1 Tg rat. Additionally, protein levels of NMDA receptor (NR2B subunit) and $GABA_AR$ ($\beta_{2,3}$ subunits) in the CPu of HIV-1 Tg rats were unaltered compared to non-Tg rats, suggesting that the number of these receptors in MSNS is unchanged. Together with our unpublished studies that found $K^{+}$ channel activity is not involved in the increased CPu neuronal firing, our findings suggest that aberrant synaptic neurotransmission, rather than independent over-activation or over-expression of intrinsic $Ca^{2+}/K^{+}$ channels, drives HIV-induced MSN hyper-excitability. Further studies are needed to determine whether the increased firing of CPu MSNs in HIV-1 Tg rats is mediated by alterations in functional activity of NMDA receptors and $GABA_A$ receptors, or by changed neurotransmission of glutamate and GABA.

**Disclosures:** **C. Khodr:** None. **L. Chen:** None. **L. Al-Harthi:** None. **X. Hu:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.02/W22

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NIH Grant R01AG021431

**Title:** Neurostructural effects of age and serostatus in treated HIV infection

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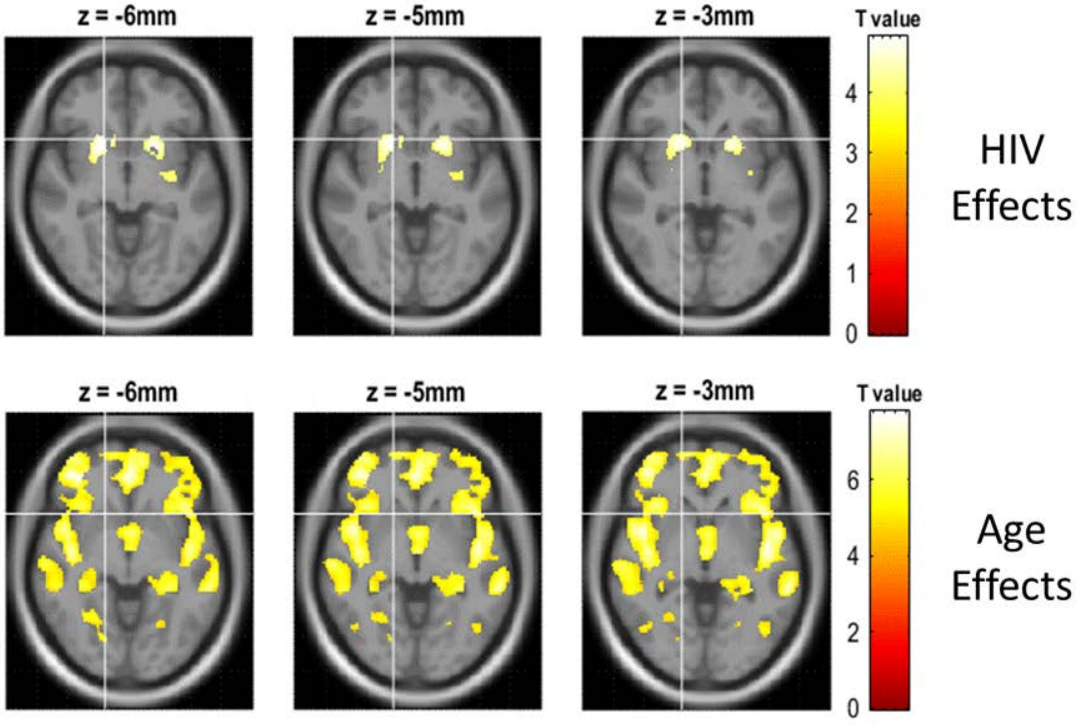
**Abstract: Purpose.** Although many studies have documented cortical and subcortical gray matter volume (GMv) changes following HIV infection, GMv is also known to decline with age and drug use. As the HIV infected population is steadily aging, the effects of age and past drug use may confound attempts to identify specific effects of serostatus on regional GMv, or to use neurostructural measures more generally in HIV diagnostic and treatment assessment contexts. In a cross-sectional study, we examined the effects of serostatus, age and past drug use on regional GMv. **Materials & Methods.** Participants included 113 seropositive and 88 seronegative men, ages 23-73, with 118 reporting past drug use. Seropositive participants were all treated with anti-retroviral therapies. Regional GMv was estimated using $1mm^3$ T1-weighted brain images. Mixed effects linear regression models were used to explore effects of serostatus, race, age, field strength, intracranial volume and drug use on regional GMv using both *a priori* regions and voxel-based morphometry. **Results.** Seropositive participants exhibited bilateral decreases in caudate and putamen GMv ($p<0.05$ FWE-corrected). Spatially independent effects of age and past drug use were also seen ($p<0.05$ FWE-corrected), with age broadly affecting numerous frontal and temporal cortical regions (Figure 1). **Conclusions.** Regional GMv is subject to additive effects of serostatus, age and past drug use, with HIV infection having neurostructural effects in the basal ganglia equivalent to 20-30 years of typical aging. Serostatus effects had high regional specificity when age and drug use were controlled, suggesting that basal ganglia GMv measured using computational neuroanatomy methods may be a useful biomarker to follow effects HIV infection and its treatment.



**Disclosures:** **E.E. O'Connor:** A. Employment/Salary (full or part-time):; University of Maryland Medical Center. **T.A. Zeffiro:** A. Employment/Salary (full or part-time):; Neurometrika. **J.T. Becker:** None. **T.A. Zeffiro:** A. Employment/Salary (full or part-time):; Neurometrika.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.03/W23

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant NS084817

NIH Grant DA033966

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**Title:** HIV-1 mediated increased striatal medium spiny neuronal excitability is associated with enhanced $K^+$ efflux and influx

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**Abstract:** Despite combined antiretroviral therapy (cART), HIV-associated neurocognitive disorders (HAND) occur in >50% of $HIV^+$ patients. The striatum is one of the key brain structures in the basal ganglia that mediates psychomotor activity and is altered by HIV-1. We previously demonstrated an abnormal hyper-excitability of mPFC pyramidal neurons in HIV-1 transgenic (Tg) rats (that express 7 of 9 HIV-1 proteins), which was associated with altered voltage-gated $Ca^{2+}$ channel function and $K^+$ efflux/influx and was independent of NMDAR activation. We assessed here the impact of HIV on GABAergic medium spiny neurons (MSNs), the predominate neurons in the dorsal striatum in 12 month-old (12m) HIV-1 Tg rats using whole-cell patch-clamp recording. We found that the majority of striatal MSNs (~75%) in non-Tg rats responded to moderate excitatory stimuli (e.g., rheobase ≤300pA; though the others showed less responses). Evoked firing was abnormally increased in the majority of MSNs in HIV-1 Tg rats compared to those from age-matched non-Tg rats. To elucidate the mechanism that underlies the hyperactivity of striatal MSNs in HIV-1 Tg rats, we assessed HIV-mediated changes in $K^+$ channel activity in these neurons. To insure that $K^+$ channel activity would not be affected by activity of other ion channels, we blocked $Na^+/Ca^{2+}$ channels, $GABA_A$ receptors and glutamate receptors. We found that voltage-sensitive $K^+$ ($K_v$) efflux was significantly increased in striatal MSNs from 12m HIV-1 Tg rats, indicating enhanced $K_v$ channel activity. Meanwhile, membrane hyperpolarization-induced $K^+$ influx was also significantly increased in MSNs from

HIV-1 Tg rats, suggesting enhanced activity of $K_{ir}$ channels (and $I_h$ channels) that leads to an increased inward rectification. However, an increased $K_v$ channel activity could render neurons less excitable; and an enhanced $K^+$ influx via $K_{ir}$ channels could decrease extracellular $K^+$ levels, which could also reduce neuronal excitability. Therefore, the HIV-induced hyper-excitability of striatal MSNs could not be attributed to these changes in $K^+$ channel activity found in this study. Additionally, we also found that the inward rectification was not altered in MSNs of HIV-1 Tg rats without blockade of GABA/glutamate receptors; and voltage-gated $Ca^{2+}$ channels were not involved in this increased firing of MSNs (unpublished data). Collectively, these findings suggest a potential involvement of GABA/glutamate neurotransmission and synaptic activity that mediates the increased MSN firing.

**Disclosures: L. Chen:** None. **C.E. Khodr:** None. **L. Al-Harthi:** None. **X. Hu:** None.

**Poster**

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**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** DA024461 (PEK)

DA034231 (PEK & KFH)

**Title:** Differences in activity-regulated cytoskeleton (Arc) expression related to HIV-associated memory and learning deficits in male and female mice

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**Abstract:** The introduction of combined and highly active anti-retroviral therapies (cART) has transitioned HIV from a disease with short-term survival into a chronic disease, and has changed the profile of HIV-associated neurocognitive disorders (HAND). While severe neurocognitive deficits leading to dementia are now rarely found, the prevalence of mild and moderate cognitive and motor deficits has remained constant or increased, even among patients with systemic viral suppression. This phenomenon likely reflects inefficient penetration of current antiretroviral drugs through the blood brain barrier, which allows the central nervous system (CNS) to exhibit low levels of persistent infection. HIV-infected patients commonly show neurocognitive deficits that affect memory, attention/concentration, mood, and fine motor skills. Furthermore, although the percentage of women in the HIV-infected population has increased, sex-related effects on memory/cognition deficits in HIV patients remain unclear. We utilized a transgenic mouse

model of HIV (conditionally expressing HIV-1 $Tat_{1-86}$ protein in CNS) and examined both males and females for changes in cognitive behavior and for expression of biochemical markers related to memory and learning, especially the Arc protein. Arc is an immediate early protein, and its expression can be induced by any environmental experience leading to learning and memory. Dysfunction of Arc-related signaling pathways is involved in disruption of memory after radiation therapy and in disease-related situations. The transient induction of Arc occurring after contemporaneous acoustic/odor stimuli was reduced by HIV-1 Tat exposure in both sexes, although Arc expression remained significantly higher in $Tat^+$ females compared to males. Somewhat parallel results were seen in a test of spatial memory (Barnes maze), since only $Tat^+$ males exhibited significant deficits. Sex-specific differences were also found in other Arc pathway proteins including CREB, Homer1 and Zif268. Our findings suggest that cognitive deficits of $HIV^+$ individuals might be influenced by sex-related differences in Arc signaling.

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**Poster**

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**Program#/Poster#:** 482.05/W25

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant DA018633

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NIH Grant DA033200

NIH Grant DA034231

**Title:** Effects of dopamine D2 receptor activation on morphine and HIV-1 Tat-induced anxiety-like and motor behaviors in a transgenic mouse model of neuroAIDS

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**Abstract:** Neurocognitive impairments such as motor dysfunction and mood disorders affect approximately 30-50% of HIV patients, despite the use of combined antiretroviral therapy (cART). Additionally, the use of opiates, whether therapeutic or recreational, can exacerbate the behavioral and morphological deficits seen in HIV-infected patients and animal models. Using a transgenic mouse with glial fibrillary acidic protein-driven *tet*-on (doxycycline) inducible CNS

expression of HIV-1 Tat, our laboratory recently showed that dopamine receptor type 2 (D2) containing medium spiny neurons (MSNs) in the striatum are selectively vulnerability to 2 weeks of HIV-1 Tat induction. Specifically, a relatively short duration (2 weeks) of HIV-1 Tat exposure increases dendritic injury and has biphasic effects on disrupting firing patterns in striatal D2 MSNs, which coincides with anxiety-like behaviors, while longer-term Tat exposure (≥ 1 month and especially 3 months) is associated with motor deficits. To investigate possible therapeutic targets to ameliorate these D2 MSN and behavioral deficits, the effects of a D2/D3 selective agonist, pramipexole (PPX), were assessed in HIV-1 Tat mice. Further, animals were given morphine (10 mg/kg, s.c.) to assess interactions of HIV-1 Tat, PPX and/or morphine. Preliminary data showed that following 2 weeks of HIV-1 Tat induction, morphine increased locomotor behavior in the open field task without reducing measures of anxiety-like behaviors, regardless of genotype. Additionally, PPX (0.1 mg/kg, i.p.) was able to block the locomotor stimulating effects of morphine. In the elevated plus maze, PPX was mildly anxiolytic both on its own and in combination with morphine. Ongoing experiments examining locomotor behavior following 4 weeks of HIV-1 Tat induction are being conducted. These data will help separate and clarify potential interactive effects of PPX and morphine on HIV-1 Tat-related alterations in locomotion versus anxiety-like behaviors. These studies will provide insight into how the dopaminergic system may affect behavioral deficits following either HIV-1 Tat and/or morphine exposure.

**Disclosures: L.K. Silva:** None. **W.D. Marks:** None. **J.J. Paris:** None. **P.E. Knapp:** None. **K.F. Hauser:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

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**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant DA013137

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NIH Grant MH106392

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**Title:** Dopaminergic and serotonergic dysfunction in HIV-1 transgenic rats: Implications for depression in HIV-1 patients

**Authors: *A. DENTON**, S. SAMARANAYAKE, R. ROSCOE, Jr., S. HARROD, H. LI, C. MACTUTUS, P. HASHEMI, R. BOOZE
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**Abstract:** HIV-1 infection is a serious condition affecting approximately 37 million individuals. Between 30% and 60% of seropositive individuals will develop symptoms of clinical depression. These individuals are five times more likely to commit suicide than non-seropositive clinically depressed patients. Dysfunction in serotonergic and dopaminergic transmission has consistently been implicated in the pathogenesis of depression. Specifically, dysfunction in the prefrontal cortex (PFC) and in the nucleus accumbens core (NAcc) region have been shown to be underlying factors in the trajectory of depression. Given these underlying neurological features, we analyzed serotonin release from the PFC and dopamine release from the NAcc using fast scan cyclic voltammetry in HIV-1 transgenic (Tg) rats. Subjects (HIV-1 Tg n=7 males/7 females; F344N n=8 males/8 females) were anesthetized and placed in a stereotaxic apparatus. For serotonin and dopamine, a stimulating electrode was implanted in the medial forebrain bundle, while carbon fiber micro-electrodes were placed in the PFC and NAcc, respectively. Biphasic pulse trains were applied through a linear constant current stimulus isolator to evaluate both serotonin and dopamine release. Both serotonergic and dopaminergic release and reuptake were impaired in HIV-1 Tg animals relative to controls. Additionally, female rodents experienced slower reuptake rates of dopamine. Collectively, these findings illustrate neurochemical factors that may potentially underlie the pathogenesis of clinical depression in HIV-1 seropositive individuals.

**Disclosures:** **A. Denton:** None. **S. Samaranayake:** None. **R. Roscoe:** None. **S. Harrod:** None. **H. Li:** None. **C. Mactutus:** None. **P. Hashemi:** None. **R. Booze:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.07/W27

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH RO1 NS083410

NIH T32 NS041218

NIH T32 NS041231

**Title:** HIV-1 Tat increases MMP-13 expression in astrocytes and promotes MCP-1 release through the MMP/PAR-1 axis

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**Abstract:** HIV-associated neurocognitive deficits (HAND) occur in up to 50% of infected individuals despite effective antiretroviral therapies. In terms of causality, infection of monocyte-derived cells (MDCs) is thought to be critical in pathogenesis. MDCs represent the predominant cell types that are infected by HIV. In the present study we focus on signaling through protease-activated receptor-1 (PAR-1) for its potential to modulate effectors of enhanced CNS entry of monocyte-derived cells. PAR-1 is a GPCR that is unique in its ability to be activated by a subset of matrix metalloproteinases (MMPs). PAR-1 can be activated by MMP cleavage of the N-terminal domain, which reveals a tethered peptide ligand. Both MMPs and PAR-1 expression are increased in the context of HAND. We observe that treatment of astrocytes with HIV-1 transactivator of transcription (Tat) protein significantly increases expression and release of MMP-13—a particularly potent PAR-1 agonist. We also observe that MMP-13 promotes astrocyte release of monocyte-chemoattractant protein-1 (MCP-1). This effect is observed to be PAR-1-dependent as astrocytes derived from PAR-1-KO mice fail to respond to MMP-13 stimulation. Interestingly, Tat's ability to increase release of MCP-1 is significantly reduced by a broad-spectrum MMP inhibitor (GM6001). Together, these results suggest that targeting the PAR-1/MMP axis may have potential therapeutic implications for HAND. Currently, PAR-1 antagonists and MMP inhibitors are being investigated in clinical trials. These results also support the possibility that in addition to transport across a damaged blood-brain barrier, MMPs may promote recruitment of MDCs through PAR-1-dependent release of MCP-1. Levels of MCP-1 have been previously shown to correlate with disease severity and recruitment of MDCs may therefore reinforce disease progression.

**Disclosures: P. Bozzelli:** None. **T. Yin:** None. **E. Wenzel:** None. **K. Conant:** None. **K.A. Maguire-Zeiss:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.08/W28

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant DA15014

NIH Grant DA32444

**Title:** *In vivo* manipulation of the CXCL12/CXCR4 signaling axis increases dendritic spine density and enhances cognitive flexibility in wild-type and HIV-Tg rats: Role of the Rac1/PAK pathway and implications for neurocognitive disorders

**Authors: *L. FESTA**[1], Y. TIAN[1], B. PLATT[1], S. B. FLORESCO[2], O. MEUCCI[1]
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**Abstract:** HIV-associated neurocognitive disorders (HAND) continue to persist despite the advent of combination antiretroviral therapy (cART). Research focus has shifted from neuronal loss, which predominantly occurred prior to the cART era, to sub-lethal synaptodendritic alterations since it is correlated with neurocognitive impairment and it may be reversible. Research conducted in our laboratory has revealed the role of the chemokine CXCL12 in several critical homeostatic processes in the CNS, including neurotransmission, pro-survival signaling, and neuronal-glial interactions. Recently, we have also demonstrated that the CXCL12/CXCR4 axis can regulate dendritic spine number on cortical neurons; however, the mechanism by which this occurs is currently unknown. Additionally, CXCL12/CXCR4 signaling is disrupted during HAND, suggesting that restoration of this pathway might alleviate cognitive deficits in HIV+ patients. In this study, we sought to determine the molecular mechanisms regulating CXCL12-mediated spine alterations, as well as whether *in vivo* administration of CXCL12 can alter dendritic spines and cognitive function in a small rodent model of HAND (HIV-Tg rat). We have demonstrated that the Rac1/PAK pathway, known to be essential for spine stabilization, is activated by CXCL12 (20 nM) in cultured cortical neurons. Furthermore, this effect is blocked by pre-treatment with the CXCR4 antagonist, AMD 3100, or the specific Rac1 inhibitor NSC23766. Since thin spines are likely targets of spine stabilization due to their transient nature, we also investigated whether particular spine morphologies are preferentially targeted by CXCL12. In cultured cortical neurons treated with CXCL12, there is a specific increase in the percentage of thin spines and a subsequent decrease in stubby ones. *In vivo* treatment of CXCL12 (25ng/5µL once per day) in WT and HIV-Tg rats significantly increased overall dendritic spine density on layer II/III pyramidal neurons in the medial prefrontal cortex (mPFC). As we observed in our *in vitro* cultures, CXCL12 treatment specifically increased thin spine density in WT and Tg rats. Importantly, rodents treated with CXCL12 displayed improvement in cognitive flexibility, as measured by an attentional set-shifting task, and this was positively correlated with dendritic spine number in the mPFC. Taken together, this study suggests that enhancement of the CXCL12/CXCR4 signaling axis may have therapeutic potential in HAND, as well as in other neurocognitive disorders characterized by synaptodendritic alterations, such as Alzheimer's and schizophrenia.

**Disclosures: L. Festa:** None. **Y. Tian:** None. **B. Platt:** None. **S.B. Floresco:** None. **O. Meucci:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

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**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant AA017347

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**Title:** Regional brain volumes in HIV infection, alcohol use disorders, and hepatitis C co-morbidity

**Authors: *N. M. ZAHR**[1,2], D. KWON[2], K. POHL[2], E. V. SULLIVAN[1], A. PFEFFERBAUM[2]
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**Abstract:** By including 4 groups of subjects, our studies are able to clearly distinguish specific from general effects of disease burden on the brain. The 4 groups included 230 control subjects, 218 individuals with Alcohol Use Disorders (AUD, E), 54 individuals infected with HIV (H), and 62 subjects comorbid for AUD + HIV (HE). SPoiled Gradient Recalled Echo (SPGR; TR=7ms, TE=2.2ms, TI=300ms, thick=1.25mm, skip=0mm, 124 slices) and dual-echo fast spin echo (FSE; TR=8583ms, TE1/2=13.5/108.3ms, thick=2.5mm, skip=0mm, 62 slices) sequences were collected on a GE 3.0T Signa whole-body system with an 8-channel phased-array head coil. After registration, skull stripping, and reformatting, regions of interest were quantified: cortical surface areas, volumes, and thickness were parcellated using FSL; white matter regions were parcellated using the SRI24 atlas. Two group comparisons showed that gray matter volume was smaller in the 3 patient groups relative to controls in frontal (E: $p=4.3e^{-12}$, H: $p=1.3e^{-09}$, HE: $p=1.9e^{-09}$), temporal (E: $p=10e^{-09}$, H: p=.01, HE: p=.007), and parietal (E: $p=1.3e^{-12}$, H: $p=3.2e^{-05}$, HE: $p=2.5e^{-07}$), but not occipital (E: p=.17, H: p=.71, HE: p=.11) cortical brain regions. The insula was also smaller in the 3 groups (E: $p=9.4e^{-06}$, H: p=.04, HE: p=.005), and all 3 groups showed an elevated number of T1 (white matter) hypointensities (E: $p=1.1e^{-08}$, H: p=.01, HE: $p=8.9e^{-08}$). The volume of the cingulate was only affected in the E and HE groups (E: p=.0001, H: p=.15, HE: p=.004); corpus callosum volume (E: p=.002, H: p=.60, HE: p=.28) was only affected in the E group. In the E and H groups, individuals with hepatitis C sero-positivity had smaller frontal gray matter volumes (t=2.86, p=.0048) and thinner frontal cortices (t=2.75, p=.0066) than sero-negative E and H participants. These data support previous findings suggesting that in these kinds of pathologies, the occipital lobes are relatively spared and indicate that the cingulate may be especially affected by addiction. Further, co-infection with hepatitis C contributes an additional burden to the brain already compromised by AUD or HIV infection.

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**Poster**

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**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant R01 MH098742

**Title:** The effect of antiretroviral therapies on oligodendrocyte growth and maturation

**Authors: *L. ROTH**[1,2,3], B. ZIDANE[3], K. L. JORDAN-SCIUTTO[3], J. B. GRINSPAN[4]
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**Abstract:** About half of HIV positive individuals develop HIV-associated neurocognitive disorder (HAND), which is a broad spectrum of cognitive, motor, and behavioral disturbances of varying severity. Combined antiretroviral therapy (cART) has led to a significant decrease in occurrence of the most severe form of HAND; however, less severe forms of the disorder have been reported to persist in 30-50% of patients. In this post-ART era, white matter pathologies are prevalent, including thinning of the corpus callosum, and reduction in white matter volumes. Moreover, white matter loss is correlated to the duration of ART exposure. Interestingly, a recent transcriptome analysis comparing untreated and ART treated patients with HAND showed downregulation of genes critical for oligodendrocyte differentiation and myelin production in patients treated with ART. These studies demonstrate that ART, as well as HIV, may perturb myelin production and oligodendrocyte growth and maturation. We have begun to study the effects of ART exposure on oligodendrocytes and their precursor cells. We hypothesize that ART compounds alter oligodendrocyte differentiation, function, and survival influencing the persistence of HAND in the post-ART era. In our lab, previous studies have shown that HIV antiretroviral compounds, lopinavir and ritonavir, both of the protease inhibitor (PI) class, inhibited oligodendrocyte precursor differentiation, while zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI), did not. New data now shows another PI, darunavir, has similar effects as ritonavir and lopinavir. Preliminary studies are now examing the newest class of HIV antiretroviral compounds, the integrase inhibitors, raltegravir and elvitegravir. These studies suggest that elvitegravir also decreased differentiation of oligodendrocyte precursors while raltegravir does not. We have also begun to test other new frontline ARTs, Tenofovir alafenamide fumarate (TAF), Preliminary data show that TAF halt oligodendrocyte precursor differentiation through decreased expression of integral myelin proteins. Investigation of the effects of these first line compounds will provide insights into the observed persistent white

matter changes seen in HAND patients with implications for their contribution to cognitive impairment.

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**Poster**

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**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH P30 MH092177

**Title:** Peripheral neuropathies (degraded myelin and reduced axons) and temperature hyposensitivity in mice that are heterozygous for Pur-alpha

**Authors: *M. F. BARBE**[1], R. LOOMIS[2], J. OTTE[2], J. P. STELMACH[3], K. KHALILI[2], J. GORDON[2]
[1]Anat. and Cell Biol., [2]Dept. of Neurosci. and Ctr. for Neurovirology, [3]Dept. of Anat. and Cell Biol., Temple Univ. Sch. of Med., Philadelphia, PA

**Abstract:** Pur-alpha is a highly conserved sequence specific DNA and RNA binding protein with established roles in DNA replication, RNA transcription and translation, cell cycle regulation, maintenance of neuronal differentiation, and regulation of myelin basic protein gene transcription. Pur-alpha expression levels are developmentally regulated and are essential for survival as knockout of the PURA gene, which encodes Pur-alpha, are homozygous lethal in the mouse model. Mutations in the PURA gene have been identified in individuals with the rare developmental disorder, PURA syndrome, which is associated with severe developmental delays, seizures, dystonia, dyskinesis, skeletal abnormalities, and delayed myelination. We recently reported that mice that are heterozygous (+/-) for Pur-alpha show cognitive deficiencies and neuropathology in the cerebellum and hippocampus, as well as decreased escape to touch responses, decreased limb tone and increased foot drags. From this, we hypothesized that there may also be peripheral nerve neuropathology. Therefore, mice that were heterozygous for Pur-alpha (+/-) were bred by crossing C57/BL6 wild type females (+/+) with heterozygous Pur-alpha (+/-) knockout males. When 9 months of age, 8 wild-type C57/BL6 mice and 5 heterozygous Pur-alpha littermates were tested for cold to hot temperature sensitivity using a temperature place preference assay. Forelimb and forepaw tissues were then collected and examined for inflammatory or myelination changes in the median and ulnar nerves and their branches in the forepaw using immunohistochemical methods. The heterozygous Pur-alpha (+/-) showed hyposensitivity to hot temperatures (41$^{o}$ and 45$^{o}$C), yet normal responses to warm, cool and cold

temperatures, compared wild type littermates. The median and ulnar nerves (examined from the forelimb into the forepaw) showed no increase in CD68-immunopositive macrophages in heterozygous Pur-alpha mice, compared to wild type mice. However, myelin disruption (Hematoxylin and eosin) and increased degraded myelin basic protein were present in the median and ulnar nerves of heterozygous Pur-alpha mice, as were decreased numbers of axon terminals to the forepaw skin. Thus, peripheral nerve neuropathology was present in heterozygous Pur-alpha mice in association with indices of forepaw hyposensitivity, yet an absence of neuroinflammatory processes.

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**Poster**

**482. Neuroinflammation: Virus and Infections I**

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**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant P30AI045008-18

**Title:** Developing an HiPSC model to study HIV-associated neurocognitive disorder

**Authors: *S. RYAN**[1], S. A. ANDERSON[2], K. L. JORDAN-SCIUTTO[1]
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**Abstract:** HIV-Associated Neurocognitive Disorder (HAND) affects 55% of HIV-infected individuals worldwide. While antiretroviral treatments have reduced the severity of HAND, the prevalence has increased due to increased life expectancy. In addition, little progress has been made in developing therapeutics to reduce the prevalence of HAND. While the major pathological manifestation of HAND is synaptodendritic damage, the full, underlying mechanism is unknown partly due to the fact that there is no *in vitro* model to study the direct interactions between HIV- infected macrophages/microglia and neurons. In order to address this problem, we have developed a human-induced pluripotent stem cell (HiPSC) based model; whereby, we separately differentiate HiPSCs into forebrain, glutamatergic-like neurons, astrocytes, and microglia-like cells and create a co-culture of the three cell types with or without HIV-infection. This novel, reductive system allows us to study the direct interactions and mechanisms by which macrophages/microglia cause synaptodendritic damage in HAND progression.

**Disclosures: S. Ryan:** None. **S.A. Anderson:** None. **K.L. Jordan-Sciutto:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.13/W33

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** MH080663

MH106967

GM081295

**Title:** SDG mediates oxidative stress and viral replication in HIV-infected human macrophages

**Authors: *K. S. WILLIAMS**[1], H. NIEVES-ROSADO[2], S. PU[2], X. WANG[4], K. L. JORDAN-SCIUTTO[3]
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**Abstract:** Macrophages and microglia (M/M) play pivotal roles in the pathogenesis of HIV associated neurocognitive disorders. The ensuing inflammatory M/M activation causes neuronal damage. Studies utilizing exogenous anti-inflammatory and antioxidants to mitigate disease progression have been unsuccessful; however, targeting endogenous antioxidant pathways such as the endogenous antioxidant response (EAR) pathway, which upregulates key antioxidant enzymes, including heme oxygenase 1 (HO-1) may be useful. In this study, we investigated the role of a flaxseed lignin, secoisolariciresinol diglucose (SDG), on oxidative stress in HIV-infected macrophages. To evaluate EAR, human monocyte derived macrophages were infected with HIV and/or SDG for 10, 30 and 60mins and immunoblotted or stained with Nrf2 to evaluate its translocation from the cytoplasm to the nucleus. Treatment of SDG alone increased Nrf2 translocation while HIV resulted in a small increase in Nrf2 translocation. Concurrent treatment with SDG and HIV exacerbated the translocation of Nrf2. Consistent with these findings, macrophages infected with HIV for one day slightly increased HO-1 expression, however, HO-1 was suppressed by peak infection. To determine if SDG can reverse the prolonged HO-1 deficits, macrophages were pretreated with SDG for 1hr prior to infection and replenished every three days. SDG treatment altered HO-1 protein levels throughout infection. Also, pretreatment of SDG partially suppressed viral replication 12 days post infection in human macrophages, assessed by a reverse transcriptase assay. Given these data, SDG increases endogenous antioxidants pathways, thereby, reducing oxidative stress and partially blocking productive infection in macrophages and may be a possible adjunctive therapeutic for HIV associated neurocognitive disorders.

**Disclosures:** **K.S. Williams:** None. **H. Nieves-Rosado:** None. **S. Pu:** None. **X. Wang:** None. **K.L. Jordan-Sciutto:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.14/W34

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** ER stress regulator ATF6b contributes to HIV-induced neurotoxicity

**Authors: *C. AKAY ESPINOZA**, P. LIN
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**Abstract:** Synaptic injury, neuronal dysfunction, and damage in patients with HIV-associated neurocognitive disorders (HAND) on suppressive antiretroviral therapy are partially driven by immune activation and chronic inflammation in response to soluble factors released by HIV-infected and/or activated macrophages as well as a low level of HIV replication in central nervous system (CNS) reservoirs. The majority of these mediators, as well as many of the comorbid conditions, can induce the ubiquitous unfolded protein response (UPR) in the endoplasmic reticulum (ER). Based on our previous results showing UPR activation in post-mortem tissue from HAND patients *in vivo,* we expanded our investigation to determine the contribution of one of the regulators of UPR in the ER, ATF6b, to HIV-induced neurotoxicity *in vitro.* Following cleavage by site-1 and site-2 proteases (S1P and S2P), ATF6b translocates to the nucleus for transcriptional induction of ER-resident chaperones, apoptotic genes, and secretory pathway regulatory genes. We found that infection of primary human monocyte-derived macrophages (MDMs) with HIV led to the nuclear translocation of the cleaved, thus active, ATF6b (N-ATF6b), which could be blocked by S1P inhibition. We also observed that blocking nuclear accumulation of N-ATF6b in macrophages by S1P inhibition led to the attenuation of death of primary rat cortical neuroglial cultures exposed to supernatants from HIV-infected MDMs (HIVMDMs). Furthermore, siRNA-mediated ATF6b knockdown in primary human MDMs led to an attenuated production of HIV p24 and reverse transcriptase activity over 15 days *in vitro* and attenuated HIVMDM-mediated neurotoxicity. These findings suggest ATF6b as a potential contributor to sustained HIV replication and subsequent release of neurotoxic factors from infected MDMs, which might impact outcomes in several cell types within the CNS of patients with HAND and illustrate ATF6b as a novel endogenous target for modulation during HIV infection.

**Disclosures:** **C. Akay Espinoza:** None. **P. Lin:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.15/W35

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** HD043680

MH106392

DA013137

NS100624

NIH T32

**Title:** HIV-1 viral proteins and Drd1α expression in medium spiny neurons of the nucleus accumbens

**Authors: *J. M. ILLENBERGER**, H. LI, S. B. HARROD, C. F. MACTUTUS, R. M. BOOZE
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**Abstract:** The dopamine (DA) system is a major target of HIV infection and contributes to the progression of HIV-1 associated neurocognitive disorder (HAND) in HIV-1+ individuals. Combination antiretroviral therapies (cART) control HIV viremia. However, HIV-1 viral proteins transactivator of transcription (Tat) and envelope glycoprotein GP120 (gp120) continue to impair DA function through mechanisms that are still unclear. The HIV-1 transgenic (Tg) rat expresses 7 of 9 HIV-1 proteins, with the exception of Gag and Pol. The current experiment classifies DA-related circuitry in HIV-1 Tg and F344/N rats by examining RNA and protein expression, as well as dendritic spine morphology of medium spiny neurons (MSNs) of the nucleus accumbens (NAc) region. Dopamine transporter (DAT), tyrosine hydroxylase (TH), and dopamine D1-alpha receptor (Drd1α) expression in D1-type MSNs of HIV-1 Tg and F344/N rats were compared by combining immunohistochemistry (IHC) and RNAscope procedures. Next, MSNs were diOlistic labeled with Helios Gene Gun (Bio-Rad) to analyze the volume, length, and distribution of dendritic spines of the NAc using Neurolucida 360 software (MBF Bioscience). HIV-1 Tg animals present altered dendritic spine lengths and distribution across branch orders of MSNs of the NAc region. We hypothesized that MSNs from the NAc region of HIV-1 Tg animals relative to controls display reduced Drd1α, DAT, and TH expression in addition to altered dendritic spine morphology due to the presence of HIV-1 viral proteins. Identifying the specific alterations that occur in dopaminergic circuitry with exposure to Tat and gp120 offers valuable insight for effectively treating cognitive decline in HIV-1+ patients.

**Disclosures:** **J.M. Illenberger:** None. **H. Li:** None. **S.B. Harrod:** None. **C.F. Mactutus:** None. **R.M. Booze:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.16/W36

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** R01 MH085607

R01 DA039044

**Title:** HIV-1 Tat impairs cognitive performance in an exposure-dependent manner

**Authors: *T. J. CIRINO**[1], J. J. PARIS[2], J. P. MCLAUGHLIN[1]
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**Abstract:** Although antiretroviral therapy (cART) has decreased the severity of Human Immunodeficiency Virus (HIV)-associated dementia, cognitive impairment and the prevalence of HIV Associated Neurocognitive Disorders (HAND) persists. The means by which HAND persists in the presence of cART in HIV+ patients remains unknown. In animal studies, exposure to the inflammatory HIV-1 regulatory protein transactivator of transcription (Tat) was found to produce cognitive learning and memory deficits. We hypothesized that brain exposure to HIV-1 Tat protein is sufficient to induce oxidative stress and neuroinflammation, ultimately impairing cognitive performance. Using the GT-tg bigenic mouse model, where brain-selective Tat expression is controlled by activation of a doxycycline (Dox) promotor, we tested the effects of Tat protein on two non-hippocampal associated cognitive tasks, the Pre-Pulse Inhibition (PPI) model of sensorimotor gating and the prefrontal cortex (PFC)-dependent Attentional Set Shift task. Western blot analysis confirmed the expression of Tat protein in GT-tg bigenic mouse brain correlated with dose and duration of Dox treatment, and magnitude of exposure to Tat protein was shown to elevate total ROS/RNS levels in whole brain homogenate assessed by a fluorophore probe assay and activate microglia in the PFC measured by Iba1 immunohistochemical labeling. Behaviorally, a 1, 7 or 14 day exposure to HIV-1 Tat protein attenuated pre-pulse inhibition. In contrast, a 7-day exposure to HIV-1 Tat protein improved certain sessions of the Attentional Set Shift associated with rule acquisition and enforcement. However, a longer exposure (14 d) reversed most improvements, and caused significant impairments in performance during intradimensional shift testing and in reversal of established compound discrimination. The role of Tat-induced neuroinflammation was confirmed through prophylactic treatment with the anti-inflammatory, indomethacin (10 mg/kg/d, i.p.). Daily

pretreatment with indomethacin concordant with Dox reversed impairment of PPI after a 1, but not 7, day exposure to Tat protein. Likewise, 14-d prophylactic indomethacin treatment prevented all Tat-induced deficits of performance in the attention set shift assay. Overall, these data suggest that expression of HIV-1 Tat protein in mouse brain was sufficient to impair cognitive performance in an exposure-dependent manner involving neuroinflammatory responses, and suggests a direct biological means by which HIV infection may promote persistent HAND and cognitive impairment in HIV patients.

**Disclosures: T.J. Cirino:** None. **J.J. Paris:** None. **J.P. McLaughlin:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.17/X1

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH- 5T32DA7234-24, DA07304

**Title:** HIV-1 envelope protein gp120 potentiates extrasynaptic GABARs

**Authors: *M. GREEN**[1,2], S. THAYER[3]
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**Abstract:** HIV-associated neurocognitive disorder (HAND) affects nearly half of the 37 million patients with HIV. Symptoms of HAND range from subclinical cognitive impairment to severe dementia. Infected cells in the brain such as microglia release viral proteins and toxins that alter neuronal function. The HIV-1 envelope protein gp120 is one such viral protein which is toxic to neurons. Using patch clamp electrophysiology in hippocampal cultures, here we describe how treatment with gp120 potentiates extrasynaptic GABA receptor (GABAR)-mediated currents. A 4 h treatment with gp120 (600 pM) significantly increased currents through extrasynaptic GABARs and this increase persisted for 24 h. Microglial release of interleukin-1β (IL-1β) likely mediates the gp120-mediated increase in GABAR currents. IL-1β directly applied to hippocampal cultures potentiated extrasynaptic GABAR currents, and inhibition of the IL-1 receptor with IL-1ra blocked gp120's effects. Furthermore, inhibition of CXCR4 on microglia with AMD3100, which is known to be upstream of IL-1β release, prevented the gp120-induced potentiation of extrasynaptic GABARs. Preliminary results show that elimination of microglia with L-Leucine Methyl Ester block gp120's effects. Preliminary results also show that α5-containing GABARs may be responsible for gp120's effects. The enhanced GABA evoked current produced by 4 h treatment with gp120 was sensitive to the α5-containing GABAR inverse agonist basmisanil. Finally, treatment with another viral protein, HIV-1 Tat (50 ng/mL) did not potentiate extrasynaptic GABARs suggesting this may be a gp120-specific effect.

Inhibition of synaptic GABARs lowers seizure threshold and induce anxiety. However, selective inhibition of extrasynaptic GABARs spares synaptic GABAR function and does not affect seizure threshold or induce anxiety. Drugs that inhibit extrasynaptic GABARs have been shown to boost cell excitability and improve cognitive function in animal models of Alzheimer's disease, stroke, and neuroinflammation. Extrasynaptic GABARs may be a promising target for the treatment of HAND.

**Disclosures: M. Green:** None. **S. Thayer:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 482.18/X2

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** VA Career Development Award BX001677

James S. McDonnell Foundation

**Title:** Inhibition of LTP in CA1 pyramidal neurons by the commonly prescribed antiretroviral, efavirenz

**Authors: *E. K. BICHLER**[1,2], P. S. GARCIA[3]
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**Abstract:** Over half of patients receiving pharmacotherapy to treat their HIV infection demonstrate some form of cognitive dysfunction. These mild impairments might be in part due to the drugs used to treat HIV infection, as recent data suggests that antiretroviral agents (ARVs) themselves may exert central nervous system (CNS) neurotoxic effects. Efavirenz, a non-nucleoside reverse transcriptase inhibitor, was associated with a decline in cognitive performance where no deficits were previously noted (Ciccarelli, Fabbiani et al. 2011) after initiation of drug treatment. Recently, our laboratory demonstrated that efavirenz conferred a detrimental effect on neuronal viability, morphology, and mitochondrial respiration in cultured rat primary cortical neurons at concentrations (20 - 50 µM) near the target plasma concentration, 6.8 µM (Ciavatta et al. 2015). To explore the potential effects of efavirenz on neurophysiologic mechanisms underlying neurocognitive tasks like learning, acutely dissociated ex vivo brain slices were exposed to study drug for 2-4 hours prior to whole cell patch-clamp recordings from CA1 pyramidal cells in the hippocampus. Theta-burst pairing (TBP) protocol (three trains of EPSPs at 5 Hz; each train consisting of 5 evoked EPSPs paired with 5 concurrent action potentials generated by somatic current injections; Rosenkranz et al. 2009) was implemented to induce

synaptic plasticity. This protocol resulted in long-term potentiation (LTP) of EPSP amplitude (mean±SD: 190±40.8%; n=15) in brain slices exposed to control conditions. Neurons subjected to 100 µM efavirenz demonstrated very little LTP by comparison (123.7±23.3%; n=8). Efavirenz concentrations at 30 µM or less did not affect synaptic potentiation. Our data suggest that although in vitro studies demonstrate detrimental effects on neuronal health at efavirenz concentrations as low as 20 µM, LTP is impaired at concentrations over ten times the target plasma concentration. Taken together, these results suggest that neurocognitive deficits associated with efavirenz treatment are not likely to result from acute network dysfunction specifically related to LTP mechanisms. It remains possible that a cumulative effect involving mitochondrial toxicity underlies the association of efavirenz with cognitive dysfunction. Future studies involving chronic administration of efavirenz to as well as an investigation of blood brain barrier permeability in an in vivo model, will aid in the understanding of the clinical consequences of ARV therapy.

**Disclosures: E.K. Bichler:** None. **P.S. Garcia:** None.

**Poster**

**482. Neuroinflammation: Virus and Infections I**

**Location:** Halls A-C

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**Program#/Poster#:** 482.19/X3

**Topic:** C.06. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** VA Career Development Award BX001677

James S. McDonnell Foundation

**Title:** Neurocognitive behavioral assessment following isoflurane anesthesia in a rat model of chronic administration of select HIV anti-retroviral drugs

**Authors: *J. FIDLER**[1], S. P. DOYLE[2], P. S. GARCIA[3]
[1]Anesthesiol., Emory Univ. / Atlanta VAMC, Decatur, GA; [2]Pharmacol., Emory Univ., Atlanta, GA; [3]Anesthesiol., Atlanta VA Med. Ctr. / Emory Univ., Decatur, GA

**Abstract:** The antiretroviral (ARV) drugs azidothymidine (AZT) and efavirenz (EFV) are commonly prescribed in treatment regimens for HIV. AZT is a nucleoside analog reverse transcriptase inhibitor (NRTI) that acts by halting viral DNA synthesis via chain termination, while EFV is a non-nucleoside reverse transcriptase inhibitor (nNRTI) that blocks the function of reverse transcriptase by directly binding with the enzyme. Whereas HIV-associated neurocognitive disorder (HAND) is a known effect of microglia and macrophage activation in the brains of HIV patients, some clinical reports have also identified mild cognitive dysfunction as a result of antiretroviral therapy (ART). However, these effects remain poorly described in

scientific literature. We have previously shown that, while AZT did not have any acute effects on neuronal viability in vitro, efavirenz may be neurotoxic through a reduction in mitochondrial respiration. Furthermore, 20 µM EFV reduced excitability of CA1 neurons in an ex vivo slice preparation. We hypothesize that any in vivo effects of ARVs on cognition may be exacerbated in the presence of an anesthetic challenge. As these drugs are often used as preventative or prophylactic agents, here, we administered clinically relevant doses of each drug to healthy, young adult Sprague Dawley rats via TID subcutaneous injection for 14 days prior to, then during, testing. On the first day of testing, rats were administered 2 hours of isoflurane (1.5% - 2.0%) or sham anesthesia (100% oxygen), followed by an emergence paradigm including time to return of righting reflex and ambulation, as well as time to attempt to remove a sticky dot placed on the forepaw. This was immediately followed by 1 hour of recording in an open field arena, then a novel object recognition (NOR) task with 24-hour intra-trial interval. AZT-treated rats given sham anesthesia showed no difference in time to remove a sticky dot, nor in NOR performance, as compared to vehicle-treated animals. However, AZT-treated rats exhibited a trend toward lower activity, including reduced exploration and grooming, in an open field arena. This ongoing research may help guide clinical decisions in those prescribing ART.

**Disclosures:** **J. Fidler:** None. **S.P. Doyle:** None. **P.S. Garcia:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.01/X4

**Topic:** C.07. Ischemia

**Support:** NIH NS086929

**Title:** Low level laser promotes cortical neurogenesis in a photothrombotic stroke model

**Authors: *L. YANG**[1,2], D. TUCKER[2], Y. DONG[2], C. WU[1], Q. ZHANG[2]
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**Abstract:** Recent work has indicated that low-level laser irradiation (LLI) may confer beneficial effects in altering the pathological status of several neurological disorders, although the underlying mechanisms are currently unclear. The current study was designed to investigate the beneficial effects of LLI on behavioral deficits and neurogenesis in a photothrombotic (PT) model of ischemic stroke in rats. Rose bengal was injected intraperitoneally (i.p.) and a cold light source was applied to exposed scalp over the right sensorimotor cortex, generating a concise and repeatable ischemic infarct. LLI treatment was performed on days 1 through 7 following PT stroke induction. Rats received i.p. injections of 5-bromodeoxyuridine (Brdu) (a cell proliferative marker) twice daily (50 mg/kg) on days 2 through 8, followed by sample collection on day 14.

Our results demonstrated that LLI significantly attenuated behavioral deficits and infarct volume after PT stroke. Further investigation revealed that LLI significantly enhanced neurogenesis as evidenced by increased expression and colocalization of Brdu, DCX, MAP2, spinophillin and synaptophysin. Mechanistic studies revealed that these beneficial effects were accompanied by a robust suppression of oxidative damage, levels of reactive gliosis, and production of pro-inflammatory cytokines. On the contrary, the release of anti-inflammatory factors, cytochrome c oxidase activity, and ATP production in peri-infarct regions were increased in LLI group animals compared with PT group controls. LLI effectively shifted activated microglia from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype, in accordance with its effect on the release of inflammatory cytokines. Our studies indicated that LLI promotes neurogenesis and improves the neuronal microenvironment by altering a broad spectrum of pathological features in ischemic conditions, including oxidative stress, mitochondrial dysfunction and neuroinflammation. These findings provide further support for the promising therapeutic effect of LLI on ischemic stroke.

**Disclosures:** **L. Yang:** None. **D. Tucker:** None. **Y. Dong:** None. **C. Wu:** None. **Q. Zhang:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.02/X5

**Topic:** C.07. Ischemia

**Support:** NRF-2014R1A2A1A11050236

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HI14C2339

NRF-2016R1A5A2012284

**Title:** The combination of DNMT inhibitor and task-specific training contributes to recovery in chronic stroke

**Authors: I.-A. CHOI**[1], *D.-H. CHOI[1], J. LEE[2]
[1]Konkuk Univ. Sch. of Med., Seoul, Korea, Republic of; [2]Rehabil., Konkuk Univ. Med. Ctr., Seoul, Korea, Republic of

**Abstract:** *Background* - Behavior and experience are capable of inducing plastic changes within the normal and injured brain. Especially, specific behavioral experience, such as motor skill training after experimental brain injury, provides functional benefit. There is currently no

specific treatment for improving functional recovery after stroke except for rehabilitation. 5-Aza-2'-deoxycytidine (decitidine) is a DNMT inhibitor. It involved in reducing extent of injury in stroke models but its effects on recovery of function are not known. The beneficial effects of early rehabilitation on neuroplasticity and functional recovery have been modeled in acute stage of experimental stroke. However, the impact of rehabilitation in chronic stage of stroke remains poorly understood. *Objectiv*e - The purpose of the study is to examine the effectiveness of the task specific training (TST) combined with decitabine as a treatment to enhance neural plasticity in the chronic stage after ischemic stroke. *Methods* - Rats underwent a photothrombosis surgery to impair sensorimotor cortex. Eight weeks after stroke, animals were trained staircase test. Before the beginning of a rehabilitation, decitabine was started to infuse in contralesional hemisphere using osmotic pump and lasted for 28 days. During the decitabine delivering, animals were exposed to TST for 4 weeks. Functional recovery was assessed using staircase test, cylinder test, modified neurological severity scores (mNSS) every 2 weeks. Biotinylated dextran amine tracing was injected into the non-lesioned forelimb sensorimotor cortex at the end of behavioral test to determine axonal plasticity in the corticorubral tract (CRT). *Results* - The TST combined with decitabine significantly improved skilled reaching ability in the staircase test at 4 weeks. Only TST group is significantly ameliorated in the mNSS scores and cylinder test at 4 weeks. Tracing the corticorubral tract, the crossing fibers from the contralesional red nucleus were significantly increased in TST and TST with decitabine groups. *Conclusion* - Functional recovery after chronic stroke may involve contralesional CRT plasticity by modulating DNA methylation in contralesional motor cortex. Our results suggest that combined therapy to enhance CRT plasticity based on TST and decitabine would constitute a promising therapy for promoting recovery of function in the chronic stage of stroke.

**Disclosures: I. Choi:** None. **D. Choi:** None. **J. Lee:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.03/X6

**Topic:** C.07. Ischemia

**Support:** CIHR

**Title:** GPR81, a novel metabolic receptor reverses brain injury following a post hypoxic-ischemic stress

**Authors: *P. M. CHAUDHARI**[1], A. MADAAN[2], X. HOU[3], I. CHARFI[3], G. PINEYRO[3], S. CHEMTOB[3]
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**Abstract: Purpose**: Premature infants are subjected to a plethora of drastic events, often leading to potential adverse consequences for neurodevelopment in addition to severe neurological insults. Although inadequate hemodynamics is an underlining feature of these encephalopathies, it is accompanied by marked neovascularization in the penumbral regions as a repair mechanism, especially for the preservation of neurons. Notwithstanding the paramount role of VEGF in post-ischemic neovascularization, other factors also partake in this process. Since vascular supply is coupled to tissue energy consumption, a role for metabolic intermediates such as lactate in angiogenesis can be surmised. We propose that lactate via its receptor GPR81 governs post-natal brain angiogenesis and is crucial during post-hypoxic ischemia (HI).
**Methods**: Changes in microvasculature were quantified using lectin staining on brain cryosections. Ex-vivo aortic explants were treated with lactate condition media from primary neuronal culture. Gene expression analysis was performed by real-time PCR. GPR81 expression was determined by immunofluorescence, lactate concentration in HI model was quantified using Lactate Assay Kit (Bio-Vision) and TTC (tetrazolium chloride) staining was used to determine the post-natal hypoxic ischemic insult in KO and WT mice.
**Results:** Intra cerebroventricular injections of lactate increased brain vascular density; no such effect was observed in GPR81 KO. GPR81 was specifically expressed on the neurons and a significant decrease (up to 20%) in vascular density was observed in the GPR81 KO as compared to age matched WT C57/BL mice. Furthermore, GPR81 regulates pro-angiogenic, angiostatic and inflammatory factors like VEGF, ANG-1, ANG-2, TSP, COX-2, TLR-4, CCL-2. Moreover, TTC staining showed an increase in infarct size in GPR81 KO mice as compared to WT mice after post-hypoxic ischemia.
**Conclusion:** The result suggests GPR81 plays a vital role in brain developmental angiogenesis and reverses brain injury in post HI mice model via regulation of various angiogenesis factors. Collectively, our study shows GPR81 is a metabolic sensor of developmental brain angiogenesis and may promote post HI recovery.

**Disclosures: P.M. Chaudhari:** None. **A. Madaan:** None. **X. Hou:** None. **I. Charfi:** None. **G. Pineyro:** None. **S. Chemtob:** None.

**Poster**

**483. Recovery After Ischemia**

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**Program#/Poster#:** 483.04/X7

**Topic:** C.07. Ischemia

**Support:** Fondation Leducq

CIHR

MSFHR

**Title:** A role for brain pericytes in cerebrovascular regeneration after stroke

**Authors: *L.-P. BERNIER**[1], J. HEFENDEHL[1], C.-A. LEWIS[2], W. SCOTT[3], L. DISSING-OLESEN[1], F. ROSSI[2], M. UNDERHILL[3], B. MACVICAR[1]
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**Abstract:** Brain pericytes are a critical component of the neurovascular unit as they are essential for the developmental maturation of cerebral blood vessels and for the integrity of the blood-brain barrier (BBB). However, their role in repairing and restoring the cerebral microvasculature following CNS trauma remains unclear, partly because their identification has traditionally relied on protein markers that are expressed in a non-specific and cell state-dependent pattern. We generated a novel transgenic mouse with highly specific and heritable expression of tdTomato in pericytes to investigate their roles following stroke *in vivo* and *ex vivo*. The mice were subjected to a photothrombotic focal stroke and the involvement of pericytes in post-stroke recovery was investigated relative to peri-lesion revascularization. We show that following initial cell death, proliferating pericytes migrate into the infarct zone where they accumulate on the ischemic side of the reactive astroglial border. Pericytes in that region drive a progressive angiogenic front that supports a wave of local tissue revascularization into the lesion, as evidenced by immature pericytes extending ramifications along vessels and associating with endothelial cells prior to functional blood flow establishment. Within a few weeks normal vessels with an intact BBB are found perfusing a previously ischemic cortical area. We provide a novel transgenic model for pericyte investigation and show that pericytes have the ability to contribute to the regeneration of cerebral blood vessels in a process that recapitulates their role in developmental vasculogenesis.

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**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

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**Topic:** C.07. Ischemia

**Support:** CONICET PIP 387

ANPCYT PICT2012-1424

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UBACYT

CONICET PIP 479

**Title:** Targeting reactive glia in brain ischemia with a G5G2.5 core-shell tecto-dendrimer

**Authors: *V. MURTA**[1], P. SCHILRREF[2], G. ROSCISZEWSKI[1], M. J. MORILLA[2], A. J. RAMOS[1]
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**Abstract:** Decreased long term disabilities after stroke are dependent on neuronal survival. Secondary neuronal death in the penumbra is facilitated by the conversion of glial cells to the proinflammatory phenotype that induces neurodegeneration. Therefore, regulation of glial activation is a compelling strategy to reduce brain damage after stroke. This regulation is challenging due to the difficulty of some drugs to access the central nervous system (CNS), and specifically target glial cells. Effective stoke therapy demands a carrier that can cross the blood-brain barrier, and target activated glial cells. Furthermore, activated glial cells (astrocytes and microglia) are a highly heterogenic population, with a broad, context dependent, spectrum of possible activation profiles. Given that different activation phenotypes can drive neuronal fate, it is important to include assorted activating stimuli. In the present work we set up to exploit the tailorable qualities of nanoparticles, and explored the use of a polyamidoamine core-shell tecto-dendrimer (G5G2.5 PAMAM) as a carrier for distinct populations of stroke activated glia. We found that G5G2.5 tecto-dendrimer is actively engulfed by glial cells in a time- and dose-dependent manner showing high cellular selectivity and lysosomal localization. In addition, *in vitro* oxygen-glucose deprivation (OGD) or lipopolysaccharide (LPS) exposure increased astroglial G5G2.5 uptake; but this was not observed in glial scar forming astrocytes. I*n vivo* brain ischemia showed an increased incorporation of the tecto-dendrimer in the lesioned area, with specific preference for immune engaged cells . We conclude that G5G2.5 tecto-dendrimer is a highly suitable carrier for targeted drug delivery to glial cells after brain ischemia.

**Disclosures: V. Murta:** None. **P. Schilrref:** None. **G. Rosciszewski:** None. **M.J. Morilla:** None. **A.J. Ramos:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.06/X9

**Topic:** C.07. Ischemia

**Support:** NIH NRSA F31 NS073149

NIH RO1 NS081055

The Dr. Miriam and Sheldon Adelson Medical Research Foundation

**Title:** Wnt7a regulation of post-stroke neurogenesis

**Authors: *H. ZHAO**[1], T. B. LENGNING[2], M. MACHNICKI[1], A. BRUMM[1], S. T. CARMICHAEL[1]
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**Abstract:** Stroke is a leading cause of adult disability, but despite its prevalence current treatments do not provide long-term recovery. Stroke itself induces a wide-range of repair mechanisms, including the proliferation and long-distance migration of immature neurons (neuroblasts) from the subventricular zone (SVZ) to peri-infarct tissue, a process termed post-stroke neurogenesis. These neuroblasts localize to and migrate along angiogenic blood vessels, forming a neurovascular niche in the peri-infarct zone. The reciprocal signaling between neuroblasts and endothelial cells has not been clearly characterized. Understanding these endogenous signaling systems may provide novel targets for pharmaceutical intervention to enhance functional recovery.
In genome-wide expression profiling studies, we identified Wnt7a as a candidate signaling gene that is down-regulated in stroke-responsive neuroblasts. Wnt7a stimulates neural stem cell proliferation and is important for neuronal differentiation and maturation in the hippocampus of adult mouse brains (Qu, et. al, 2013). However, its role in post-stroke neural repair is not well understood. In previous studies, Wnt7a has been shown to promote angiogenesis, resulting in increased vessel density, endothelial cell proliferation, and blood brain barrier maturation after stroke. Based on these findings, Wnt7a may play a key role in the neural repair by promoting neural progenitor proliferation and maturation. Here, we identify Wnt7A's role in post-stroke neurogenesis in a set of gain-of-function (GOF) and loss-of-function (LOF) studies in the photothrombotic stroke model using lentiviral vectors for overexpression and microRNA-mediated knockdown of Wnt7a in the peri-infarct cortex.

**Disclosures: H. Zhao:** None. **T.B. Lengning:** None. **M. Machnicki:** None. **A. Brumm:** None. **S.T. Carmichael:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.07/X10

**Topic:** C.07. Ischemia

**Support:** ECRF2014

**Title:** Effects of chronic administration of the selective histamine $H_4$ receptor antagonist JNJ7777120 on cerebral injury in a model of transient brain focal ischemia in the rat

**Authors: I. DETTORI**[1], L. GAVIANO[1], A. MELANI[1], L. LUCARINI[1], *G. PEPEU[2], E. MASINI[1], F. PEDATA[1]
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**Abstract:** Cerebral ischemia is a multifactorial pathology characterized by different events evolving in time. The acute injury, characterized by a massive increase of extracellular glutamate levels, is followed by a secondary brain injury that develops from hours to days after ischemia. Histamine is a neurotransmitter/ neuromodulator in the Central Nervous System (CNS). Recently, it was demonstrated in the experimental model of focal cerebral ischemia induced by occlusion of the middle cerebral artery (MCAo) in the rat, the levels of histamine, evaluated by microdialysis, increase in the ischemic areas. The human histamine $H_4$ receptor is the most recently discovered member of the G protein-coupled receptor subfamily of histamine receptors. It is predominantly expressed in several cell types of immune system and in numerous areas of the CNS including cortex and striatum.
The aim of our study was to assess the putative neuroprotective effects of the potent and selective histamine $H_4$ receptor antagonist, JNJ7777120, chronically administered (1 mg/kg, i.p., twice/day for 7 days) on damage parameters in a model of focal ischemia induced in the rat by the transient (1 hour) occlusion of the MCA (tMCAo) by the monofilament technique.
Chronic treatment with the histamine $H_4$ receptor antagonist, JNJ7777120, significantly protected from the neurological deficit 1, 5 and 7 days after tMCAo (score at 7 day: 3.5±0.5, n=10 versus 5.8±0.4, n=13 in vehicle group; $p<0.001$) and significantly reduced the body weight loss at 5 and 7 days after tMCAo with respect to vehicle-treated rats (respectively $p<0.05$; $p<0.01$). Seven days after the ischemic insult, JNJ7777120 reduced the volume of the ischemic cortical damage (16.6±2.18 $mm^3$, n=10 versus 28.7±1.83 $mm^3$, n=10 in vehicle group; $p<0.0005$) and the volume of the ischemic striatal damage (4.2±0.47 $mm^3$, n=10 versus 10.1±1.14 $mm^3$, n=10 in vehicle group; $p<0.0001$). Seven days after ischemia, chronic treatment with JNJ7777120, significantly reduced the number of $IBA1^+$ (specific for microglia) and $GFAP^+$ (specific for astrocytes) cells in the ischemic core and boundary zones of striatum and cortex with respect to vehicle-treated rats. JNJ7777120 also decreased the plasma levels of the proinflammatory cytokines, IL-1β and TNF-α seven days after tMCAo.
Results demonstrate that the selective antagonist of histamine $H_4$ receptor JNJ7777120, systemically and chronically administered after ischemia, reduces the ischemic brain damage and improves the neurological deficit, suggesting that the $H_4$ histamine receptor is a valuable pharmacological target after brain focal ischemia.

**Disclosures: I. Dettori:** None. **L. Gaviano:** None. **A. Melani:** None. **L. Lucarini:** None. **G. Pepeu:** None. **E. Masini:** None. **F. Pedata:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.08/X11

**Topic:** C.07. Ischemia

**Support:** NS056839

**Title:** Axonal remodeling induced by rehabilitative training on the isometric pull task after middle cerebral artery occlusion in the rat

**Authors: *K. S. VALENZUELA**[1], S. LANGNER[2], M. BLAKER[2], S. BREWER[2], T. A. JONES[1], T. SCHALLERT[1]
[1]Psychology, The Univ. of Texas At Austin, Austin, TX; [2]Univ. of Texas at Austin, Austin, TX

**Abstract:** Reaching tasks are commonly used to assess various facets of paretic forelimb function and the influence of motor rehabilitative training in rat stroke models. Behavioral manipulations such as reach training can influence patterns of neural connectivity post-stroke. It has yet to be determined how reach training influences patterns of axonal reinnervation in the lesioned hemisphere after strokes that cause subcortical damage. Long Evan rats were trained with their preferred limb to reach outside a chamber, grasp a handle, and pull to receive a food pellet (Isometric Pull task, Vulintus). Transient focal ischemia (60 mins) was induced in the hemisphere contralateral to the preferred limb by an intraluminal middle cerebral artery occlusion suture method. Rats received either six weeks of rehabilitative training (RT) with the paretic limb (n=8) or non-training control procedures (n=6) on the Isometric Pull task. Forelimb strength, as measured in grams, and the number of trials completed during 30 min sessions were probed weekly for seven weeks. At the completion of the behavioral study, all animals received an axon tract tracer (biotinylated dextran amine) via pressure injection in layer V motor cortex in the ipsilesional hemisphere. The tracer was allowed to travel for 21 days and then brains were harvested. Prior to ischemic induction, animals reached with an average of 192.40g and completed an average of 160 trials per 30 minute session. Average forelimb force dropped to 79.02g and average trials per session dropped to 29 at an initial one week post-stroke assessment. Animals were then assigned to either RT or a control group. After 1 week, forelimb force was similar for the RT group (88.46±29.62g) and control group (75.36±24.41g). However, the groups' performance began to steadily separate at the week 2 time point. The RT group (111.28±28.33g) was able to reach with twice as much force as the control group (53.64±24.69g) at week 2. By week 6, the RT group (135.02±22.93g) reached with about two and a half times as much force as the control group (55.94±27.45g). A similar temporal pattern of group differences was found in the measure of trials completed per session. After 1 week, the RT (74.00±21.90) and control (64.00±21.49) groups had similar performance. By week 6, the RT group

(100±16.23) completed nearly 4 times as many trials per session as the control group (28.00±14.14). Thus, rehabilitative training on the Isometric Pull task resulted in major improvements in paretic forelimb strength and performance. Work to examine the influence of rehabilitative training on axonal reinnervation of regions denervated by the MCAo damage is ongoing. All data are mean±SEM.

**Disclosures: K.S. Valenzuela:** None. **S. Langner:** None. **M. Blaker:** None. **S. Brewer:** None. **T.A. Jones:** None. **T. Schallert:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.09/X12

**Topic:** C.07. Ischemia

**Support:** Academy of Finland Grants 250275, 256398, 281394

Biocentrum Helsinki

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**Title:** Intranasally delivered recombinant MANF protein reduces infarction volume and promotes recovery in a rat cortical stroke model

**Authors: *J. E. ANTTILA**[1], K. MÄTLIK[1], O. S. MATTILA[2], P. LINDHOLM[1], P. J. LINDSBERG[2], M. AIRAVAARA[1]
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**Abstract:** Introduction: Mesencephalic astrocyte-derived neurotrophic factor (MANF) is an 18 kDa endoplasmic reticulum (ER) resident protein that is upregulated and secreted upon ER stress, and has neurotrophic properties. Intracranial delivery of MANF provides neuroprotection in rat models of ischemic stroke. Our aim was to test if non-invasive intranasal delivery of MANF is neuroprotective and determine the pharmacokinetic profile of MANF after intranasal administration.
Methods: Unilateral cortical infarction was induced in adult male Sprague Dawley rats by transiently ligating the distal branch of the right middle cerebral artery with a 10-0 suture and occluding both common carotid arteries for 60 minutes. Recombinant human MANF (rhMANF) or vehicle was administered intranasally before the induction of ischemia and immediately after reperfusion in all experiments. Effects on infarct volume were measured 48h post-stroke (n=10-17). In separate experiments, behavioral recovery was monitored for 14 days (Bederson's score,

body asymmetry test and measurement of locomotor activity [n=14-15]). The distribution of rhMANF after intranasal delivery was investigated using $I^{125}$-rhMANF and an enzyme-linked immunosorbent assay (n=6), and the effect of rhMANF on ischemic and post-ischemic cerebral blood flow (CBF) was evaluated with Laser Doppler Flowmetry (n=9-10).
Results: Intranasally administered rhMANF decreased infarction volume by 30% ($p<0.05$) and reduced neurological deficits measured on days 7 ($p<0.05$) and 14 ($p<0.0001$) post-stroke. No significant differences were found between the treatment groups in CBF during occlusion or reperfusion. One hour after intranasal delivery 0.4% of the total dose of $I^{125}$-rhMANF reached systemic circulation and only 0.003% was detected in the brain.
Conclusions: Our results show that rhMANF is neuroprotective also when administered intranasally, providing reduced infarct volumes and improved functional recovery. Further investigation is warranted to determine the individual contribution of circulating and intracerebral rhMANF in these effects.

**Disclosures: J.E. Anttila:** None. **K. Mätlik:** None. **O.S. Mattila:** None. **P. Lindholm:** None. **P.J. Lindsberg:** None. **M. Airavaara:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.10/X13

**Topic:** C.07. Ischemia

**Support:** Strategic Priority Research Program of the Chinese Academy of Sciences (XDB02020002)

**Title:** Extended therapy time window in rat model of ischemic stroke by salvianolic acid a

**Authors: *N. J. LI**, C. JIAO, L. XU
Kunming Inst. of Zoology, Yunnan, China

**Abstract:** Acute ischemic stroke (AIS) is a leading cause of death and disability in middle and aged population. Major challenge is to extend the time window (< 3-4.5 hours) of using tissue plasminogen activator (tPA) and to preserve the penumbra for functional recovery after AIS. We here report that treatment of salvianolic acid a (SAA) at the time up to 8 hours after AIS-like brain injury is markedly beneficial, and that with higher doses or longer delay (12 hours) is intriguingly harmless. A novel mechanism of SAA is attributable because co-treatment with tPA leads to synergic efficacy in aged rats, and because SAA enhances transdifferentiation of reactive astrocytes into neurons in the penumbra and promotes recovery from long-lasting impairment of spatial memory and glucose metabolism. Our data suggest a novel mechanism of SAA

underlying neuroprotection and compatibility with tPA, relevant to the development of a novel-generation of agents for treating AIS.

**Disclosures:** **N.J. Li:** None. **C. Jiao:** None. **L. Xu:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.11/X14

**Topic:** C.07. Ischemia

**Support:** SanBio Inc., California, US

Sunovion Pharmaceuticals, Inc., a wholly owned subsidiary of Sumitomo Dainippon Pharma Co., Ltd.

**Title:** Sensorimotor & fine motor skill deficits were chronically sustained in mild ischemic stroke rats

**Authors: *A. N. SATO**, Z. WARRAICH, E. MORADI, D. BATES, Y. ANDREWS-ZWILLING
Res. and Develop., SanBio, Inc., Mountain View, CA

**Abstract:** In rodent models of ischemic stroke, loss of function can be variable over prolonged periods of time and mild impairments can be difficult to detect depending on the extent of the stroke. In this study, we investigated several behavioral outcome measures for a mild stroke model in rats, which showed sustained deficits in sensorimotor and fine motor skilled tasks up to 1.5 months. The present study assessed behavioral deficits of rats 7, 21, 28, 35, 42 and 49 days following 120 minutes of transient Middle Cerebral Artery occlusion (MCAo) using a 0.33 mm filament in the left hemisphere. Deficits were assessed by sensorimotor and locomotor behavioral tests: Rotarod test, Paw Whisker test, Akinesia (Stepping) test, and Isometric Pull test. The Isometric Pull test, an updated method of the reach-to grasp task, is automated and incorporates accurate quantitative force generation, pull attempts, and success rate to assess forelimb function in rats (Hays et al., 2012). Rats were highly proficient in all the behavioral assays prior to stroke. There were no significant differences between non-stroke and stroke rats in the Stepping and Rotarod tests, which assessed gross motor skills. However, a sustained trend of sensorimotor deficit in the impaired forelimb (right whisker stimulation, right paw placement) and in the cross-midline (left whisker stimulation, right paw placement) in the Paw Whisker test was observed in mild stroke but not observed in non-stroked rats. In addition, rats with mild stroke showed sustained deficits in mean peak force and % successful hits in the Isometric pull test and maintained fine motor deficits compared to the non-stroked group. The force generated

from the impaired right paw in the mean peak force was substantially decreased in all rats after stroke. The frequency of reaching the minimal reward threshold of 120 g ratio to number of attempts were decreased in all stroke rats post-operatively. Deficits for both Paw Whisker and Isometric Pull Test were sustained 49 days following lesion. Fine functional and sensorimotor behavioral assays, such as the Isometric Pull and Paw Whisker test, were able to detect sustained long-term functional impairments compared to gross locomotor behavioral assays in mild stroke rats.

**Disclosures: A.N. Sato:** None. **Z. Warraich:** None. **E. Moradi:** None. **D. Bates:** None. **Y. Andrews-Zwilling:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.12/DP06/X15 (Dynamic Poster)

**Topic:** C.07. Ischemia

**Support:** NIH Grant T32 NS069562

The Beatrice Menne Haggerty Center for Research on Brain Injury and Repair in Stroke

**Title:** The effects of increasing activation of cholinergic neurons in the nucleus basalis on stroke recovery

**Authors: *A. BECKER**[1], D. BETZ[2], M. P. GOLDBERG[3]
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**Abstract:** Cholinergic long-range projections from the nucleus basalis (NB) are important for learning and cortical plasticity. In rats, electrical stimulation of the NB timed with sensory or motor activity increases the size of task-relevant cortical maps and increases performance after training. We tested the hypothesis that increasing the firing of cholinergic NB neurons during rehabilitative motions can increase the extent or speed of recovery after stroke. Using a mouse line that expresses cre in cholinergic cells under control of the choline acetyltransferase promoter, we injected a cre-dependent Gq DREADD (Designer Receptors Activated by Designer Drugs) or control GFP virus bilaterally into the nucleus basalis of C57/BL6 mice. Stroke-related behavioral deficits were measured using the automated reach task (Becker et al, J Neurosci Meth, 2016) before and up to 1 week after stroke. The DREADD-activing drug clozapine-N-oxide was injected before rehabilitative sessions from weeks 2-6 and final performance evaluated on week

7. Preliminary results show a trend toward greater improvement at week 7 after stroke in the DREADD-injected mice; results and methods for increasing effect size will be discussed.

**Disclosures: D. Betz:** None. **M.P. Goldberg:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.13/X16

**Topic:** C.07. Ischemia

**Support:** Marga und Walter Boll-Stiftung (#210-12-12 and #210-10-15)

Köln Fortune Program/Faculty of Medicine, University of Cologne, Germany (#13/2014 and #339/2015).

**Title:** Bioluminescence imaging visualizes osteopontin-induced neurogenesis and neuroblasts migration in the mouse brain after stroke

**Authors: *M. SCHROETER**[1], R. ROGALL[1], A. BACH[1], A. PIKHOVYCH[1], S. U. VAY[1], J. BAERMANN[1], M. HOEHN[2], S. COUILLARD-DESPRES[3], G. R. FINK[1,4], M. A. RUEGER[1]
[1]Dept. of Neurology, Univ. Hosp. Cologne, Cologne, Germany; [2]Max-Planck-Institute for Metabolism Res., Colgne, Germany; [3]Paracelsus Med. Univ., Salzburg, Austria; [4]Inm-3, Res. Ctr. Juelich, Juelich, Germany

**Abstract:** Osteopontin (OPN), an acidic phosphoglycoprotein, is upregulated in the brain after cerebral ischemia. We previously reported OPN to support migration, survival, and proliferation of neural stem cells (NSC) in primary cell culture, as well as their differentiation into neurons. We here analyzed the effects OPN on neuroblasts *in vivo* in the context of cerebral ischemia. Transgenic mice expressing luciferase (luc) under the control of the neuroblast-specific doublecortin- (DCX-)promotor, allowing visualization of neuroblasts *in vivo* using bioluminescence imaging (BLI), were injected with OPN intracerebroventricularly (n=8), control mice were injected with vehicle-buffer (n=8). To assess the effects of OPN after stroke, additional mice were subjected to photothrombosis, and injected with either OPN (n=14) or vehicle (n=13). OPN enhanced the migration of neuroblasts both in the healthy brain as well as after stroke, as quantified by BLI *in vivo*. Moreover, the number of neural progenitors was increased following OPN-treatment, with maximum effects on 2 days after OPN-injection into the healthy brain, and 14 days after OPN-injection following stroke. After stroke, OPN quantitatively promoted the endogenous, ischemia-induced neuroblast expansion, additionally recruiting progenitors from the contralateral hemisphere. Data suggest OPN as a promising substance for the targeted activation of neurogenesis in future preclinical stroke studies.

**Disclosures:** **M. Schroeter:** None. **R. Rogall:** None. **A. Bach:** None. **A. Pikhovych:** A. Employment/Salary (full or part-time):; A.P. is now an employee of BAyer AG, Leverkusen, Germany. **S.U. Vay:** None. **J. Baermann:** None. **M. Hoehn:** None. **S. Couillard-Despres:** None. **G.R. Fink:** None. **M.A. Rueger:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.14/X17

**Topic:** C.07. Ischemia

**Support:** NS090904

**Title:** Effects of 3K3A APC on subcortical white matter stroke in mice

**Authors: *Y. WANG**, Z. ZHAO, A. MONTAGNE, B. V. ZLOKOVIC
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**Abstract:** Subcortical white matter stroke constitutes up to 30% of all stroke subtypes, occurs initially as silent infarcts in the white matter (WM), and contributes significantly to the development of vascular dementia. Activated protein C (APC) is a plasma serine protease that is capable of antithrombotic, anti-inflammatory, anti-apoptotic, and cell-signaling activities. 3K3A-APC, a recombinant variant of APC with reduced anticoagulant activity, engineered to reduce APC-associated bleeding risk while retaining normal cell-signaling activity, have shown benefits in preclinical models of ischemic stroke with big infarct involved common large artery and gray matter. In this study, subcortical WM stroke model was induced by vasoconstrictor N5 (1 iminoethyl) L nornithine, dihydrochloride (L Nio). L Nio (Calbiochem) was injected into subcortical WM of the anterior cingulum (AC) of the corticolimbic circuit or the subcortical white matter ventral to the mouse forelimb motor cortex using the Neurostar motorized ultra precise small animal stereotaxic instrument (Model 963SD). Mice received 0.2 mg/kg intravenously of recombinant murine 3K3A APC or saline at 4, 24, 48 and 72 h after stroke. The results showed that 3K3A APC significantly reduced the lesion volume and protected blood brain barrier damage 3 days after stroke, and improved remote memory function 4 weeks after stroke, compared to vehicle. These results demonstrated that 3K3A APC might be an effective treatment for white matter stroke.

**Disclosures:** **Y. Wang:** None. **Z. Zhao:** None. **A. Montagne:** None. **B.V. Zlokovic:** None.

**Poster**

**483. Recovery After Ischemia**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 483.15/X18

**Topic:** C.07. Ischemia

**Support:** NIH Grant R21NS094881

**Title:** Casein kinase 2 inhibition promotes white matter recovery after ischemia

**Authors: *S. BRUNET**, C. BASTIAN, D. AQUILA, S. BALTAN
Cleveland Clin. Fndn., Cleveland, OH

**Abstract:** Ischemic stroke is the third leading cause of death globally and axonal injury and dysfunction are responsible for much of the disability observed following a stroke. Human brain comprises equal proportions of gray matter and white matter. White matter is injured in most strokes and contributes to the behavioral deficits following a stroke. Casein kinase 2 (CK2) is expressed in brain, including white matter, and is regulated by ischemia. We therefore hypothesized that transient CK2 inhibition would protect white matter (WM) from ischemic injury. To assess the impact of CK2 inhibition on axonal electrical activity following oxygen glucose deprivation (OGD), mouse optic nerves (MONs), a pure white matter track, from C57BL/6J were subjected to OGD (1h) while eliciting compound action potentials (CAPs) when exposed to either CX-4945, a selective CK2 inhibitor, or control artificial cerebrospinal fluid (ACSF). We observed that CX-4945 preserved CAPs when applied either before or after OGD. Then to determine the impact of CK2 inhibition on glial cell survival following OGD, MONs exposed to OGD treated with either CX-4945 or control ACSF were processed for immunohistochemistry. We observed that CX-4945 treatment protected oligodendrocytes from OGD. To determine if CK2 inhibition protected mitochondrial from OGD, MONs from Thy-1 mito-CFP mice were similarly subjected to OGD in the presence of CX-4945 or control ACSF. We observed that CX-4945 maintained Thy-1 mito-CFP fluorescence following OGD. Lastly, to determine which signaling pathway CK2 employed to protect axonal function against OGD we tested the role of AKT and CDK5 signaling. We observed that MK-2206 and roscovitine, selective AKT and CDK5 inhibitors respectively, protected WM function only when applied before OGD. Overall, we demonstrated that CK2 inhibition preserves axonal function by preserving oligodendrocytes and mitochondrial function following ischemic injury. Also, we showed that AKT and CDK5 signaling likely contribute to the protective mechanism conferred by CK2 inhibition on WM functional recovery from ischemia. We suggest that CK2 inhibitors, which are currently in phase I-II clinical trials for cancer therapy could be repurposed and provide a novel therapeutic target for ischemic stroke patients.

**Disclosures:** **S. Brunet:** None. **C. Bastian:** None. **D. Aquila:** None. **S. Baltan:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.01/X19

**Topic:** D.03. Somatosensation: Pain

**Title:** Lamina I spinoparabrachial neurons: Sensitization to noxious stimuli in rats with chronic constriction injury of the sciatic nerve and poor response to pregabalin

**Authors: *J. ALLARD**[1], C. LE CUDENNEC[2], V. CASTAGNÉ[2]
[1]E-Phys, Clermont-Ferrand, France; [2]Porsolt S.A.S., Le Genest-Saint-Isle, France

**Abstract:** Chronic constriction injury (CCI) induced by loose ligation of the sciatic nerve results in robust behavioural mechanical and thermal hypersensitivity in rats. The aim of the present work was to assess 1) whether electrophysiological recordings of spinoparabrachial neurons could evidence this hypersensitivity and 2) the impact of acute pregabalin treatment on the responses of these neurons in CCI and SHAM rats. Spinoparabrachial neurons receiving C fibre input and innervating the glabrous skin of the hind paw were recorded under isoflurane anaesthesia. Spontaneous activity and evoked responses to mechanical (von Frey probe (VF), calibrated pinch) and thermal (water jet (WJ)) stimuli were measured on the side ipsilateral to the surgery in 20 CCI rats and SHAM rats (1 neuron per rat). After this initial characterisation, responses to pinch and water jet at 50 °C were assessed before and after the i.v. delivery of 30 mg/kg pregabalin or the corresponding vehicle, for 60 min post-injection. Behavioural testing confirmed the existence of a significant hypersensitivity to mechanical and thermal stimulations in the CCI rats compared with SHAM rats in advance of their use for electrophysiology. The search of neurons was based exclusively on antidromic stimulation from the parabrachial area. Seventeen and 20 neurons responding to inclusion criteria were initially characterised in SHAM and CCI rats respectively (median conduction velocity, 13 m/s, range, 4.7-22.2 m/s, n=37). Twenty five out of the 29 recovered recording sites were located in lamina I. Spontaneous activity was virtually inexistent. Thermal responses were significantly increased in CCI rats compared with SHAM rats (p=0.007, 0.041, 0.051 and 0.040 for WJ at 0, 42, 46 and 50 °C, Mann-Whitney test, respectively). Responses to pinch (p=0.013, Mann-Whitney test) but not to VF 400, 600 and 800 mN were also significantly increased in CCI rats compared to SHAM rats. The effect of pregabalin or the corresponding vehicle on responses to pinch and WJ 50 °C was completed in 7 SHAM and 8 CCI rats. In the present conditions, there was no evidence of any inhibitory activity of pregabalin 30 mg/kg at 20, 40 or 60 min post-injections. Thus, evoked responses confirmed the sensitization of lamina I spinoparabrachial neuron to noxious stimuli in rats with CCI, in agreement with previous reports. In the present experimental conditions, pregabalin 30 mg/kg failed to decrease responses of lamina I spinoparabrachial neuron to noxious stimuli.

**Disclosures:** **J. Allard:** None. **C. Le Cudennec:** None. **V. Castagné:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.02/X20

**Topic:** D.03. Somatosensation: Pain

**Support:** National Nature Science Foundation of China (81572859)

Chinese National Program on Key Basic Research Project (973 Program) (2014CB910303 )

Shanghai Collaborative innovation center(TM201521 )

**Title:** The molecular mechanism of acid sensitive ion channel mediated pain in promoting the proliferation of breast cancer cells

**Authors:** ***C. YANG**[1], G. DING[2]
[1]Xinhua Hosp. Chongming Br., Shanghai City, China; [2]Shanghai Intl. Med. Ctr., Shanghai, China

**Abstract:** Abstract:
Background: Cancer pain seriously affects the life quality of patients with tumor. Our previous research indicated that relieve of pain availably prolong the survival period of patients with advanced cancer. However, the mechanism about how pain impact cancer is still unclear. A novel kind of ion channels - acid sensing ion channels (ASICs), are widely participate into the initiation and development of pain. Earlier studies have shown that the acid sensitive ion channels also are high expression in a variety of tumor cells. These results show acid sensitive ion channels are likely to involve with both tumor and pain. ASICs might be important role which contribute to the impact of pain to cancer.
Result: In this research, Based on our cancer biobank and pain biobank, there are 30 tumor tissues of breast cancer patients were chosen and grouped according to the patient's pain rating, a rat cancer pain model was established by sciatic nerve ligation of a rat with tumor. Through a combination of cell and molecular biology, immunochemistry, electrophysiology, animal behavior testing, system illustrate the following three results: 1) The alteration of distribution and property of ASIC1a underlying cancer pain, the expression of ASIC1a increases as the patient's pain level increases; 2)The influence of cell factor in microenvironment to ASIC1a, the result of high - throughput cytokine microarray detection show that the expression of cytokines in patients with severe pain was higher than that in painless patients, After receiving analgesic treatment, the expression of tumor cytokines decreased in patients with severe pain; 3) The mechanism of

ASIC1a mediating breast tumor development induced by pain. Inhibition of or interfering with the expression of ASIC1a in pain tumor rats compared with painless tumor rats can significantly inhibit tumor growth.
Conclusion: The up-regulation of tumor cytokines in tumor microenvironment increase the up-regulation of ASIC1a expression in patients with cancer pain, and the increase of ASIC1a expression promotes the proliferation of tumor cells.
Significance: It is expected to enrich the hypothesis “Pain – Microenvironment - Cancer”, and explore the potential of ASIC1a as a key therapeutic target for cancer and pain.

**Disclosures: C. Yang:** None. **G. Ding:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** D.03. Somatosensation: Pain

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Grants NASU #67/15-H to PB

**Title:** Encoding of acute nociception by specific population of lamina I projection neurons

**Authors: K. AGASHKOV**[1], V. KROTOV[2], M. KRASNIAKOVA[1], B. V. SAFRONOV[4], *N. V. VOITENKO[3], P. BELAN[2]
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**Abstract:** Spinal lamina I projection neurons (PNs) are key elements of the pain processing system, which relay peripheral input to supraspinal structures generating sensation of pain. The population of PNs is small (~5% of lamina I neurons) but very heterogeneous according to their intrinsic and synaptic properties. For this reason, we know little about how the nociceptive peripheral input integrated by the spinal neuron network is finally encoded by PNs in a form of modality-specific discharge patterns. Here, whole-cell recordings were done in an intact spinal cord preparation with attached dorsal roots to examine the input-output characteristics of lamina I PNs retrogradely-labeled from the lateral PB area. We identified a specific group of PNs (16%)

having high action potential (AP) output to the supraspinal structures in a response to nociceptive dorsal root stimulation. In these high output PNs (HO-PNs), a stimulation of nociceptive afferents evoked gradual strength-dependent amplification of synaptic input expressed as an increase in the number of generated APs. Upon a root stimulation at C-fiber-intensity, the HO-PN group generated more than 80% of APs of the entire population of lamina I PNs, thus, being the major group of PNs codifying acute pain sensation. We have also identified several mechanisms of this nociceptive input amplification. First, HO-PNs are strongly and selectively innervated by the high-threshold Adelta- and C-afferents providing robust and reliable spike generation. Second, the nociceptive input was amplified by intrinsic bursting capabilities of HO PNs. Third, the afferent input was prolonged (to 0.-1.5 s) and potentiated (to -45 mV to -20 mV) by the NMDAR-dependent synaptic component forming intrinsic plateau potentials generated by HO-PNs. The afferent stimulation increased, for several seconds, spontaneous excitatory drive to HO-PNs that became suprathreshold during the plateau potential and evoked an additional series of network-driven APs. In conclusion, we have described a new type of lamina I PNs efficiently transmitting the main part of primary nociceptive input to supraspinal structures playing an important role in acute pain generation. A complex interplay between synaptic, intrinsic and network activities underlies unique nociceptive encoding features of this group of PNs.

**Disclosures: K. Agashkov:** None. **V. Krotov:** None. **M. Krasniakova:** None. **B.V. Safronov:** None. **N.V. Voitenko:** None. **P. Belan:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.04/X22

**Topic:** D.03. Somatosensation: Pain

**Support:** 2016R1D1A1B03934932

**Title:** Anti-nociceptive effect of dexmedetomidine co-administered with lidocaine in a mouse orofacial inflammatory pain model

**Authors: J. YEO**[1], S. YOON[2], S. KIM[1], *D. ROH[1]
[1]Dept. of Oral Physiol., Kyung Hee Univ., Seoul, Korea, Republic of; [2]Dent. Res. Inst., Seoul Nat'l Univ., Seoul, Korea, Republic of

**Abstract:** Although the administration of dexmedetomidine (DEX), an alpha-2 adrenoceptor agonist, significantly attenuates nociception and hyperalgesia in several pain models, the clinical trial of DEX is limited by several side effects including drowsiness, hypotension and sedation. The present study aims to determine whether intraperitoneal injection of DEX suppresses the nociceptive responses in a mouse orofacial inflammatory pain model, and whether it affects

motor coordination and blood pressure. Moreover, we examined whether co-administration of lidocaine with ineffective dose of DEX produced an anti-nociceptive effect without side effects. The 5% formalin (10$\mu l$) was subcutaneously injected into the right upper lip, and the rubbing responses were counted for 45 minutes. DEX (3, 10, 30 or 100$\mu$g/kg) were treated 30 min before formalin injection. DEX (10$\mu$g/kg) reduced inflammatory nociceptive responses in the second phase. However, higher dose (30, 100$\mu$g/kg) of DEX totally blocked the formalin induced nociceptive responses in both the first and the second phases, which was likely to be associated with a sedative effect of DEX. The high dose of DEX (30$\mu$g/kg) significantly reduced the motor performance in the rotarod test. In addition, both blood pressure and heart rate also decreased in the high dose of DEX-treated mice. On the other hand, when the lidocaine (0.5%) alone was subcutaneously injected, the nociceptive responses in the first phase, but not in the second phase were reduced. Interestingly, although lower dose of DEX (3$\mu$g/kg) did not reduce nociceptive responses, the co-administration with lidocaine potently suppressed the nociceptive responses in both the first and the second phases without a significant side effect. These results suggest that co-administration of DEX with lidocaine can be a safe therapeutic strategy for orofacial inflammatory pain management.

**Disclosures:** **J. Yeo:** None. **S. Yoon:** None. **S. Kim:** None. **D. Roh:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.05/X23

**Topic:** D.03. Somatosensation: Pain

**Title:** Electrophysiological characteristics of SP-mediated antinociception in muscle nociceptors

**Authors: *C.-T. CHANG**[1,2], C.-H. LEE[2], C.-C. CHEN[1,2]
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**Abstract:** Fibromyalgia is a disease that causes chronic widespread muscle pain without apparent tissue damage or nerve injury. Animal models of that mimic the chronic muscle pain syndromes of fibromyalgia can be induced by intermittent cold stress (ICS) or dual intramuscular acid injection. Previous data have shown intramuscular acid injection activates acid-sensing ion channel 3 (ASIC3) to depolarize muscle nociceptors and results in the development of chronic muscle pain. Interestingly, intramuscular acid signaling also induces SP release and mediates an antinociceptive effect in muscle nociceptors, by which SP specifically enhances M-type potassium current and attenuates ASIC3-induced inward current on most gastrocnemius muscle (GM) afferent dorsal root ganglion (DRG) neurons. However, the role of ASIC3 in SP-mediated antinociception, especially in chronic pain context, is still unknown. Due to the fact that ICS-

treated ASIC3 knockout mice develop chronic widespread pain, we can explore the role of ASIC3 in SP-mediated anti-nociceptive signaling. We hypothesize ASIC3 could contribute to SP-mediated anti-nociception in ICS model. Here, we conducted whole-cell patch clamp recordings of medium-size (30-40μm) GM afferent DRG neurons. We applied [Sar9,Met(O2)11]-Substance P (SM-SP), a synthetic peptide analog of SP, to stimulate the patched neurons and characterized 3 different SM-SP-induced (outward current, inward current and no response). The result showed that SM-SP-induced outward current ($I_{SP\text{-}O}$) in about 35% of GM afferent DRGs. Also, we found 85.71% GM afferent DRGs with $I_{SP\text{-}O}$ showed salicylic acid-sensitive acid(pH6.8)-induced inward current indicating the expression of ASIC3. We further evaluated the expression of $I_{SP\text{-}O}$ in muscle afferent DRG neurons of ICS- and non-ICS-treated WT mice and found the population of neurons with $I_{SP\text{-}O}$ was decreased in ICS-treated mice as compared with that of WT mice. However, ASIC3 KO did not change the neuron population that express $I_{SP\text{-}O}$ in ICS and non-ICS treated mice. The result suggests that ICS-treated mice may partially cause the deficit of SP-signaling, whereas the SP-signaling is independent of ASIC3.

**Disclosures: C. Chang:** None. **C. Lee:** None. **C. Chen:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.06/X24

**Topic:** D.03. Somatosensation: Pain

**Support:** NIH grant NS080889

**Title:** Effects of neonatal vincristine administration on spinal nociceptive processing in the developing rat

**Authors: *K. A. SCHAPPACHER**[1], M. L. BACCEI[2]
[1]Univ. of Cincinnati Dept. of Anesthesiol, Cincinnati, OH; [2]Univ. of Cincinnati Dept. of Anesthesiol., Cincinnati, OH

**Abstract:** Vincristine (VNC) is commonly used to treat pediatric cancers, including the most prevalent childhood malignancy, Acute Lymphoblastic Leukemia. While clinical evidence suggests that VNC causes peripheral neuropathy in children, the degree to which pediatric chemotherapeutic regimens influence nociceptive signaling throughout life remains unclear, in part due to the lack of an established animal model of chemotherapy-induced neuropathic pain during early life. Therefore, the present study investigated the effects of neonatal VNC exposure on pain sensitivity in the developing rat. In addition, given that noxious sensory experience during the neonatal period can evoke persistent changes in synaptic function within spinal nociceptive circuits, we investigated the degree to which early life VNC modulates synaptic

transmission in the superficial dorsal horn (SDH).
Male and female Sprague Dawley rats received a total of five i.p. injections of 60 µg/kg VNC, or equivalent volumes of saline, over a ten day period starting on postnatal day (P)11. VNC-treated rats of both sexes demonstrated significantly lower mechanical withdrawal thresholds compared to control groups beginning at P26 which persisted throughout the first eight weeks of life. To determine if the onset of VNC-induced mechanical hypersensitivity is accompanied by an imbalance of excitatory and inhibitory synaptic transmission within the SDH, we used whole-cell patch clamp techniques to record miniature excitatory and inhibitory postsynaptic currents (mEPSCs and mIPSCs) from lamina I projection neurons in rat spinal cord slices at P26-P30. VNC treatment did not significantly influence the functional properties of excitatory or inhibitory synaptic signaling onto the key output neurons of the spinal nociceptive network. Overall, the present results demonstrate that VNC evokes a mechanical hypersensitivity in rats that is slow to emerge during adolescence and may not depend on a dramatic reorganization of the synaptic circuits within the developing spinal SDH.

**Disclosures: K.A. Schappacher:** None. **M.L. Baccei:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.07/X25

**Topic:** D.03. Somatosensation: Pain

**Title:** Measuring anxiety- and depression-like behaviors in a mouse model of neuropathic pain is critically dependent on the testing environment

**Authors: *H. H. AHN**, S. MARTINEZ GONZALEZ, S. HONG, T. WILSON, Y. CARRASQUILLO
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**Abstract:** Chronic pain is associated with mood disorders such as anxiety and depression. The effects of pain on affective behaviors in current mouse models of persistent pain, however, have been controversial due to inconsistency and limited reproducibility between laboratories. Several groups have reported increases in anxiety-like and depression-like behaviors using the elevated zero maze, the open field test and the forced swim test following placement of a cuff around the sciatic nerve. However, using the same behavioral tests and pain models, our initial experiments were unable to detect changes in affective behaviors between sham and nerve cuffed mice 5-13 weeks following surgery, in spite of the clear presence of tactile hypersensitivity, measured using von-Frey filaments. Our inability to measure changes in affective behaviors was not due to the specific time-point tested or the specific mouse strain selected. Experiments performed at several time-points following the sham or cuff surgery and in several mouse strains and C57 substrains

also failed to detect differences in affective behaviors between sham and cuff groups. Given the convincing positive published data, we undertook a systematic evaluation of the testing conditions and found that the presence of robust pain-induced changes in affective behaviors in the nerve cuff model is highly dependent on the precise environmental testing conditions. The testing conditions that we found were critical to measure pain-related changes in affective behaviors were: specific testing apparatus, room lighting, color of the walls surrounding the testing apparatus, and water temperature during the forced swim test. Importantly, the optimal testing conditions worked when the test was performed by both male and female experimenters. In addition, the results from our experiments further revealed that different mouse strains require different environmental testing conditions to detect affective behavioral changes, likely reflecting strain-dependent differences in baseline levels of anxiety- and depression-like behaviors. Altogether, our results validate the use of the nerve cuff neuropathic pain model to measure pain-related changes in affective behaviors in mice and further demonstrate that these behaviors are highly dependent on the environmental testing conditions used. Ongoing experiments in the laboratory aim at identifying the brain mechanisms underlying the onset and expression of pain-related affective behaviors at the circuit and cellular level using molecular genetics, chemogenetic and optogenetic approaches.

**Disclosures: H.H. Ahn:** None. **S. Martinez Gonzalez:** None. **S. Hong:** None. **T. Wilson:** None. **Y. Carrasquillo:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.08/X26

**Topic:** D.03. Somatosensation: Pain

**Title:** Role of macrophage derived exosomes in inflammatory pain

**Authors: *R. JEAN-TOUSSAINT**, S. RAMANATHAN, Y. TIAN, H. HU, S. AJIT
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**Abstract:** Chronic inflammatory pain ensues when the normal process of inflammation does not resolve, resulting in excess proinflammatory cytokines and chemoattractants that can eventually lead to central sensitization. Neuroimmune signaling links peripheral neuronal injury or inflammation with the activation of central nervous system neuroglial cells, resulting in sustained neuronal hyperexcitability. Exosome-mediated transfer of biomolecules to acceptor cells constitutes a novel mechanism of cell-to-cell communication. Exosomes are 30-100 nm membrane vesicles that carry mRNAs, miRNAs and proteins to recipient cells via circulation. Exosome uptake results in modulation of gene expression in recipient cells. Exosomes derived from antigen-presenting cells such as dendritic cells and macrophages are capable of inducing

therapeutically relevant adaptive immune responses, but the mechanistic basis of this protection is not well understood. In a previous study, we have shown that exosomes secreted by RAW 264.7 macrophages after lipopolysaccharide (LPS) stimulation can upregulate three miRNAs known to have immunomodulatory effects. Moreover, a single intraplanar injection of exosomes derived from LPS stimulated RAW 264.7 cells attenuated thermal hyperalgesia in the complete Freund's adjuvant (CFA) mouse model of inflammatory pain. Here, we sought to determine the mechanistic basis of anti-inflammatory effects of macrophage-derived exosomes using primary mouse neurons and microglia in vitro. Our preliminary data shows efficient uptake of exosomes by both neurons and microglia. However, gene expression changes in microglia was more robust following exosome uptake when compared to neurons. Additionally, an intrathecal injection of exosomes into CFA model mice reversed mechanical but not thermal sensitivity. These data indicate that gene expression changes induced by exosomal uptake differ between neurons and microglia, and the route of administration of exosomes can influence inflammatory pain-induced nociceptive behavior in mice.

**Disclosures: R. Jean-Toussaint:** None. **S. Ramanathan:** None. **Y. Tian:** None. **H. Hu:** None. **S. Ajit:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.09/X27

**Topic:** D.03. Somatosensation: Pain

**Support:** NIH NCCIH Intramural

**Title:** Sexually motivated hedonic behavior is related to persistent pain-induced stress in male rats

**Authors: *M. H. PITCHER**[1,2], F. TARUM[2], M. LEHMANN[3], M. C. BUSHNELL[2]
[1]NIH, Bethesda, MD; [2]Pain and Integrative Neurosci. Laboratory, Natl. Ctr. for Complementary and Integrative Health, Natl. Inst. of Hlth., Bethesda, MD; [3]Natl. Inst. of Mental Health, Section on Functional Neuroanatomy, Lab. of Cell. and Mol. Regulation, Natl. Inst. of Hlth., Bethesda, MD

**Abstract:** Anhedonia, or the loss of interest in previously rewarding or pleasurable activities such as sexual activity, is a diagnostic criterion for major depressive disorder. In male rodents, scent marking of urine from pro-estrous females is a hedonic behavior that is sensitive to stressors such as social defeat. Considering that depression is often comorbid with chronic pain in humans and depressive-like behavior may also be seen in rodent models of persistent pain, we tested (i) how urine scent marking behavior in rodents is altered in persistent inflammatory pain

states, and (ii) if scent marking behavior relates to post-injury outcomes such as pain and stress. We compared urine scent marking behavior in rats (n=12/group) at baseline and one, two and three weeks after unilateral sham injection or intra-articular injection of Complete Freund's Adjuvant (CFA), known to elicit profound deficits in weight bearing on the ipsilateral paw for at least three weeks. Male rats were allowed to scent mark in a large arena with an absorbent paper floor containing a spot of urine harvested from pro-estrous female rats. Marking preference for the female urine zone was calculated in relation to the amount of marking in the remaining arena, where a preference score >1 represents a preference for the female urine zone and a preference <1 represents a preference for the remaining arena.
At baseline, all rats exhibited robust marking preference for the female urine zone, where marking preference for the CFA and sham groups were not significantly different (2.83±0.29 and 2.57±0.25, respectively). Marking preference was unchanged one and two weeks after CFA. However, by three weeks the CFA group exhibited a significantly reduced marking preference (1.56±0.26, *p=0.015*) as well as increased plasma corticosterone (1362.0±156.2pg/ml vs 676.7±88.7pg/ml in shams; *p=0.002*). While post-injury marking preference was not associated with pain, stress or pre-injury (basal) marking preference, a significant positive correlation between basal marking preference and post-injury corticosterone levels was found (R=-0.58, p=0.03), suggesting that higher basal hedonic behavior may be protective against persistent pain-induced stress.
Together, our findings indicate (i) that urine scent marking behavior may represent an ethologically relevant assay supporting translational research of persistent pain-induced depression, and (ii) that post-injury stress responsiveness may be related to pre-injury bio-psycho-social factors.

**Disclosures: M.H. Pitcher:** None. **F. Tarum:** None. **M. Lehmann:** None. **M.C. Bushnell:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.10/X28

**Topic:** D.03. Somatosensation: Pain

**Title:** Physiological contribution of genetically-distinct cells of the central amygdala in the modulation of tactile hypersensitivity in a mouse model of neuropathic pain

**Authors: *T. WILSON**, H. AHN, S. VALDIVIA, A. KHAN, S. MARTINEZ GONZALEZ, Y. CARRASQUILLO
Natl. Ctr. for Complementary and Integrative Hlth., NIH, Bethesda, MD

**Abstract:** Increasing evidence over the last 15 years supports the critical contribution of the central nucleus of the amygdala (CeA) to the modulation of pathological pain and its related affective comorbidities. Previous studies have demonstrated that neurons in the CeA are genetically diverse. More importantly, recent advancement in our ability to selectively manipulate the activity of genetically-defined neurons has revealed differential contributions of distinct CeA neuronal subtypes to emotional behaviors. However, the genetic identity of the CeA neurons that are recruited during pain and contribute to the modulation of pain-related behaviors, remains unknown. The experiments here began to address these questions by using a combination of molecular genetic, chemogenetic, electrophysiological, behavioral and histological approaches. To induce persistent tactile hypersensitivity, we used the sciatic nerve cuff and the Complete Freund's Adjuvant (CFA) rodent paradigms, as models of neuropathic and inflammatory pain respectively. The combined results from our experiments specifically demonstrate that there are at least three functionally distinct populations of nociceptive neurons in the CeA: 1) a population of "pain ON" cells that becomes hyperexcitable in the context of persistent pain; 2) a second population of "pain ON" cells that undergoes pain-induced plasticity; and 3) a population of "pain OFF" cells that becomes hypoexcitable in the context of pain. *In vivo* selective chemogenetic inhibition of either of the "pain ON" cell populations decreased tactile hypersensitivity in models of persistent pain, demonstrating that activation of these cells is necessary for pathological tactile hypersensitivity. In contrast, *in vivo* selective inactivation of the "OFF cells" in naïve animals induced tactile hypersensitivity in the absence of injury, demonstrating that inactivation of these cells is sufficient to induce tactile hypersensitivity. Altogether, the results from our experiments provide the first causal evidence for the existence of "pain ON" and "pain OFF" cells in the CeA that are genetically-distinct and have opposing contributions to the modulation of peripheral tactile hypersensitivity in models of persistent pain.

**Disclosures: T. Wilson:** None. **H. Ahn:** None. **S. Valdivia:** None. **A. Khan:** None. **S. Martinez Gonzalez:** None. **Y. Carrasquillo:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.11/X29

**Topic:** D.03. Somatosensation: Pain

**Support:** FAPESP Grant 15/09888-0

FAPESP fellowship 16/04848-2

**Title:** Sleep pattern evaluation in adult rats submitted to nociceptive neonatal stimulation

**Authors: *J. M. MALHEIROS**[1], C. AMARAL[1], J. C. MUNIZ[1], L. RODRIGUES[1], L. COVOLAN[2]
[1]Univ. Federal De Sao Paulo, São Paulo, Brazil; [2]Physilogy, Univ. Federal De Sao Paulo, Cleveland, Brazil

**Abstract:** Invasive painful procedures are often performed in infants admitted to intensive care units. The acute and long-term effects of these stimuli can be investigated in animal models, such as in newborn rats. Previous studies have shown that animals undergoing nociceptive stimulation in the neonatal period do not display adequate physiological manifestations when facing stressful events in adulthood. This indicates that stressful experiences at critical periods of development may mitigate the mechanisms of stress resilience. Based on this, the aim of this study is to investigate the sleep (macro and microarchitecture) parameters in the baseline, post-challenge and sleep deprivation (homeostatic response) conditions in adult rats that underwent neonatal nociceptive stimulation (induced on the first or eighth postnatal day, with CFA - complete Freund's adjuvant intraplantar injection). The animals were submitted to two days of sleep recording (2 × 24 h), classified as basal. After that, the animals were challenged with a stressor agent to evaluate the sleep homeostatic response to stress. The movement restriction was performed for two hours so that the sleep of these animals was evaluated for another 24 h. After one week, the animals went through a baseline (2 × 24h) and were submitted to total sleep deprivation using the gentle handling method for 6 h, in order to verify the expression of the sleep homeostatic response to deprivation. Briefly, the data obtained with the sleep record were: total sleep time, total REM (Rapid Eye Movement) sleep time, total low-amplitude sleep time in NREM (no REM) sleep, total high-amplitude wave sleep time in NREM sleep, total number of episodes in REM sleep, total duration time of REM sleep episodes, total wake time, total active waking time, total quiet waking time. All data are being analysed in male and female rats. To date, in the light phase, the females P8 group presented higher sleep time of high amplitude waves when compared to the control group, both at baseline and post-restriction ($P<0.05$). In addition, P8 female group had lower REM sleep time when compared to P1 and control female groups in the post-restriction light phase ($P <0.05$).

**Disclosures: J.M. Malheiros:** None. **C. Amaral:** None. **J.C. Muniz:** None. **L. Rodrigues:** None. **L. Covolan:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.12/X30

**Topic:** D.03. Somatosensation: Pain

**Title:** Effects of chronic exposure to tumor necrosis factor on pain-related behavior and sodium channel gene expression in dorsal root ganglion neurons

**Authors: M. E. O'LEARY**, A. BOTTARO, I. KUZIN, C. HO, *B. D. FISCHER
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**Abstract:** The goal of these studies was to investigate the links between chronic exposure to the pro-inflammatory cytokine tumor necrosis factor (TNF), hyperalgesia and the excitability of dorsal root ganglion (DRG) sensory neurons. We employed transgenic mice that constitutively express TNF (TNFtg mice), a well-established model of chronic systemic inflammation. At 6 months of age, TNFtg mice demonstrated increased sensitivity to both mechanical and thermal heat stimulation relative to aged-matched wild-type controls. These increases in stimulus-evoked behaviors are consistent with nociceptor sensitization to normal physiological stimulation. The mechanisms underlying nociceptor sensitization were investigated using single-cell analysis to quantitatively compare gene expression in small-diameter (<30 μm) DRG neurons. This analysis revealed the upregulation of mRNA encoding for tetrodotoxin-resistant (TTX-R) sodium ($Na^+$) channels (Nav1.8, Nav1.9), $Na^+$ channel β subunits ($\beta_1$ - $\beta_3$), TNF receptor 1 (TNFR1) and p38α mitogen-activated protein kinase in neurons of TNFtg mice. Whole-cell electrophysiology demonstrated a corresponding increase in TTX-R $Na^+$ current density, hyperpolarizing shifts in activation and steady-state inactivation, and slower recovery from inactivation in the TNFtg neurons. Increased overlap of activation and inactivation in the TNFtg neurons produces inward $Na^+$ currents at voltages near the resting membrane potential of sensory neurons (i.e. window currents). The combination of increased $Na^+$ current amplitude, hyperpolarized shifts in $Na^+$ channel activation and increased window current predicts a reduction in the action potential threshold and increased firing of small-diameter DRG neurons. Together, these data suggest that increases in the expression of Nav1.8 channels, regulatory $\beta_1$ subunits and TNFR1 contribute to increased nociceptor excitability and hyperalgesia in the TNFtg mice.

**Disclosures: M.E. O'Leary:** None. **A. Bottaro:** None. **I. Kuzin:** None. **C. Ho:** None. **B.D. Fischer:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.13/X31

**Topic:** D.03. Somatosensation: Pain

**Support:** National Nature Science Foundation of China 81400905

National Nature Science Foundation of China 81572859

Chinese National Program on Key Basic Research Project 2014CB910303

**Title:** The experimental and clinical study: Persistent pain could be a potential stimulus on tumor

**Authors: *F. JIANG**[1], *F. JIANG[1], J. LI[2], G. DING[3]
[1]Xinhua Hosp. Chongming Br., Shanghai, China; [2]Xinhua Hosp., Shanghai Jiao Tong Univ. Sch. of Med., Shanghai, China; [3]Shanghai Intl. Med. Ctr., Shanghai, China

**Abstract:** With the progress in diagnosis and treatment techniques, the survival of patients with tumor has been much prolonged. However, for the Lack of health knowledge, many penitents are still suffering from various persistent pain. Recent studies revealed that persistent pain does not only affect the quality of life or bring great mental pressure to the patients, but also may promote tumor recurrence and metastasis. Our study established two pain models to explore the potential impact of pain on the tumor. In the first model, we mimicked neuropathic pain by sciatic nerve ligation on rats with tumor. The mechanical pain response threshold was lower in the trial group than in the control group ($p<0.05$). Seven days later, we found that the rats weight of the trial group were significantly lower than those in the control group ($p<0.001$). Besides, the tumor weight of the trial group was higher than that of the control group ($p<0.05$). The tumor volume of trial group was also larger compared with control group ($p<0.05$). In another animal model, we mimicked tumor cell bone metastasis induced pain on rat. We found that the tumor volume and weight of trial group at day 7, 10 and 14 was significantly higher than those of the control group ($p<0.05$). Clinical observations showed more valuable results. We counted the clinical data of 57 patients with advanced hepatocellular carcinoma and found that the median survival period of patients who received effective pain relief is 5.0 months (95% CI, 1.210 to 5.234), which is much longer than painful patients (3.0 months, 95% CI , 0.1911 to 0.8261). Therefore, both animal and patient research suggested that persistent pain is not symptom only. Long term pain might be a deathful threat for cancer patients.

**Disclosures:** **F. Jiang:** None. **J. Li:** None. **G. Ding:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.14/X32

**Topic:** D.03. Somatosensation: Pain

**Support:** PhRMA Foundation Starter Grant

Iowa Osteopathic Education and Research Funds

**Title:** Chronic pain state mediates development of renal inflammatory response

**Authors: *V. DURIC**[1], B. DUONG[1], M. CARDER[1], G. CROSBY[1], V. BABICH[1,2], F. DI SOLE[1]
[1]Physiol. and Pharmacol., Des Moines Univ., Des Moines, IA; [2]Mercy Col. of Hlth. Sci., Des Moines, IA

**Abstract:** Chronic pain state and related stress can correlate to the development of mood disorders and disease of peripheral organs, such as kidney disease, via chronic systemic inflammation and elevation of proinflammatory cytokines. Chronic pain is one the most distressing symptoms among patients with chronic kidney disease (CKD). The prevalence of chronic pain in CKD patients has been associated with development of depressive symptoms, while major depression episodes have been linked with a substantially increased risk of death. This clinical evidence suggests that an effective treatment of chronic pain-related stress and depression may reduce mortality in people with CKD. This study aims to determine whether an immune reaction is the mechanism that links depressive behavior induced by chronic pain and anomalies of kidney function. The neutrophil gelatinase-associated lipocalin (NGAL) and IL-18 are early diagnostic inflammatory biomarkers. They accumulate in the kidney in response to inflammation, kidney injury and decreased kidney function. Protein levels of NGAL and IL18 were analyzed by immunocytochemistry in animals exposed to chronic pain that have developed depressive-like behavioral phenotype. NGAL and IL18 protein levels were significantly increased in rat models of neuropathic (spared nerve injury) and inflammatory (injections of complete Freund's adjuvant) pain when compared with their controls; a prevalent increase in NGAL and IL18 protein levels was measured in the inflammatory pain model (~40% increase in both glomeruli and tubules, quantified using novel MATLAB algorithm). These observations suggest that chronic pain and related stress effects induce renal inflammation and possibly a reduction in kidney function. Ongoing studies aim to determine whether chronic stress *per se* mediates a similar inflammatory response in the kidney. In summary, this study might support a mechanistic understanding of a bidirectional pathway between chronic pain related-stress and kidney dysfunction.

**Disclosures: V. Duric:** None. **B. Duong:** None. **M. Carder:** None. **G. Crosby:** None. **V. Babich:** None. **F. Di Sole:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.15/X33

**Topic:** D.03. Somatosensation: Pain

**Support:** JSPS KAKENHI Grant Number JP16K15337

**Title:** Involvement of beta2-microglobulin and transient receptor potential vanilloid 1-expressed primary afferent neurons in uremic pruritus

**Authors: *T. ANDOH**, T. MAKI, S. LI, D. UTA
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**Abstract:** Uremic pruritus is an unpleasant symptom in patients undergoing hemodialysis, and the underlying mechanisms remain unclear. In patients undergoing hemodialysis, the concentration of plasma β2-microglobulin (β2-MG), which is well-known as an MHC class I molecule, is increased. In this study, we investigated whether β2-MG was a pruritogen. Intradermal injections of β2-MG into the mouse rostral back elicited hind paw scratching in the injected site and the surroundings. In addition, intradermal injection of β2-MG into the cheek also elicited scratching, but not wiping. β2-MG-induced scratching was inhibited by the μ-opioid receptor antagonist naltrexone hydrochloride. These findings suggest that β2-MG-induced scratching is an itch-related response. β2-MG-induced scratching was not inhibited by antagonists of itch-related receptors (e.g., H1 histamine receptor, TP thromboxane receptor, BLT1 leukotriene $B_4$ receptor, and proteinase-activated receptor 2) activated the factors released from keratinocytes or mast cells. However, β2-MG-induced scratching was attenuated in mice desensitized by repeated application of capsaicin. In addition, β2-MG induced phosphorylation of extracellular signal-regulated kinase (a marker of activated neurons) in primary culture of dorsal root ganglion neurons that expressed transient receptor potential vanilloid 1 (TRPV1). These results suggest that β2-MG is a pruritogen and elicits itch-related responses, at least in part, through TRPV1-expressing primary sensory neurons.

**Disclosures: T. Andoh:** None. **T. Maki:** None. **S. Li:** None. **D. Uta:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.16/Y1

**Topic:** D.03. Somatosensation: Pain

**Support:** NIH NCCIH Intramural

**Title:** No evidence for social contagion of itch in mice observing histamine-injected demonstrators

**Authors: *J. LILJENCRANTZ**[1,2], M. H. PITCHER[2], L. A. LOW[2], L. BAUER[2], M. C. BUSHNELL[2]
[1]NCCIH, Natl. Inst. of Hlth., Bethesda, MD; [2]Pain and Integrative Neurosci. Laboratory, Natl. Ctr. for Complementary and Integrative Health, Natl. Inst. of Hlth., Bethesda, MD

**Abstract:** It is recognized in humans and other primates that the sensation of itch does not require the presence of a pruritogen; contagious itch can be induced simply by observing others engaged in scratching behavior. Here, we investigate the existence of itch contagion in mice using histamine injected (sub-cutaneous, nape of neck, 500µg histamine) demonstrator mice exhibiting scratching behavior. Adult male C57BL6 mice (n=44) were used in the experimental conditions (i) Un-injected observer (n=12) adjacent to a histamine-injected demonstrator (n=12), (ii) Two un-injected mice adjacent to each other (n=12), (iii) Un-injected control mice tested alone (n=8). Test chambers were separated by a transparent wall allowing for visual contact (auditory/olfactory transmission possible through mesh floor).
Our data analysis included three behavioral quantification methods to assess contagious itch in un-injected observers but failed to provide supportive evidence for the existence of this phenomenon in mice. (1) *Total scratching*: total scratching bouts in 30 min. Scratching bouts of un-injected observers next to histamine-injected demonstrators (2.0±0.6) was indistinguishable from that of un-injected observers next to un-injected demonstrators (3.3±0.6) or mice tested alone (1.5±0.6; H(3)=4.372, *p=0.112*). There was no association between total scratching bouts of un-injected observer with that of histamine-injected demonstrators (r=0.02, p=0.96). (2) *Temporally contiguous scratching:* scratching bouts within 30 secs following demonstrator scratching, regardless of if the observer was facing the demonstrator or not. We found no difference in temporally contiguous scratches in un-injected mice observing histamine-injected mice (0.5±0.2) compared to those observing un-injected mice (0.5±0.3; $X^2$=0.75,1(24), *p=0.387*).
Finally, in light of the recent publication by Yu et al. (2017. Science. 355:1072-1076) presenting support for contagious itch in mice, behavioral quantification was also scored according to their method (3) *Imitative scratching*: observer scratching bouts within 5 secs of pausing (~1 sec) and looking at the demonstrator mouse scratching. However, none of our 12 un-injected observers paired with histamine injected demonstrators exhibited this scratching behavior and only 1 of 12 un-injected observer mice paired with an un-injected demonstrator scratched (between groups not significant: X2=1.04,1(24), p=0.307).
Taken together, we find no evidence supporting the occurrence of itch contagion in mice. Our inability to replicate the findings of Yu et al. may depend on differences in the itch model used for the demonstrator mice.

**Disclosures: J. Liljencrantz:** None. **M.H. Pitcher:** None. **L.A. Low:** None. **L. Bauer:** None. **M.C. Bushnell:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.17/Y2

**Topic:** D.03. Somatosensation: Pain

**Support:** NIH NS055860

NIH NS045594

**Title:** Role of $Na_V1.6$ and $Na_V\beta4$ sodium channel subunits in the rat back pain model induced by chronic compression of the lumbar dorsal root ganglia

**Authors: *J. A. STRONG**, W. XIE, J. ZHANG, J.-M. ZHANG
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**Abstract:** Hyperexcitability of sensory neurons plays a key role in initiating pain behaviors in several different rodent chronic pain models. Previously, we have shown that the sodium channel subunit $Na_V1.6$ and its modulatory subunit $Na_V\beta4$ play important roles in the pain behaviors and sensory neuron hyperexcitability (especially repetitive firing) induced by local inflammation of the dorsal root ganglion (DRG) with the immune stimulator zymosan. In this study we examined the role of these subunits in another, commonly used model of low back pain in which the L4 and L5 DRG are chronically compressed by small metal rods (CCD model). This results in sensory neuron hyperexcitability and marked mechanical and cold hypersensitivity. The L4 and L5 DRG were injected with previously validated siRNA constructs directed against either $Na_V1.6$ or $Na_V\beta4$ just prior to DRG compression in rats of both sexes. Control rats were injected with a non-targeting siRNA. Knockdown of either $Na_V1.6$ or $Na_V\beta4$ reduced CCD-induced static mechanical allodynia (von Frey test), dynamic mechanical allodynia (withdrawal to stroking of the paw with a fine cotton wisp), cold allodynia (withdrawal to acetone stimuli) and guarding behavior of the ipsilateral paws. Reduced mechanical pain behaviors were observed for the entire time course of the experiment (4 weeks), likely outlasting the duration of protein knockdown by the single siRNA injection. Overall the two siRNA constructs gave similar results, and results were similar to those obtained in the DRG inflammation model although the reduction in mechanical pain behaviors was not quite as complete in the CCD model and reduction in cold pain behaviors was more robust in the CCD model. Upregulation of the $Na_V1.6$ in the compressed DRG (70% increase on postoperative day 3) was observed with immunohistochemical methods, as previously reported for the DRG inflammation model. An additional similarity between the CCD and DRG inflammation models was that in both models pain behaviors were remarkably reduced by prior “microsympathectomy”, i.e., by cutting the grey rami bringing sympathetic postganglionic fibers to the L4 and L5 DRG and spinal nerves. Previously, we have observed that both the CCD and the DRG inflammation model cause increased pro-inflammatory cytokines and decreased anti-inflammatory cytokines as measured by protein multiplexing in the DRG. It will be of interest to examine the cytokine profiles in these models after knockdown of $Na_V1.6$ or $Na_V\beta4$, in order to determine which cytokines are directly regulated by the local inflammatory signals, and which also depend on changes in neuronal excitability.

**Disclosures:** **J.A. Strong:** None. **W. Xie:** None. **J. Zhang:** None. **J. Zhang:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.18/Y3

**Topic:** D.03. Somatosensation: Pain

**Support:** University of Arizona startup funds

**Title:** Long-lasting antinociceptive effects of green light in rats and humans

**Authors: *M. M. IBRAHIM**[1], A. PATWARDHAN[1], K. GILLBRAITH[1], J. HANSON[1], A. MOUTAL[2], W. LI[2], S. CAI[2], L. A. CHEW[3], X. YANG[5], A. DORAME[3], T. P. MALAN[1], T. W. VANDERAH, Ph.D.[4], F. PORRECA[6], R. KHANNA[2]
[1]Univ. of Arizona Dept. of Anesthesiol., Tucson, AZ; [2]Pharmacol., [4]Phamarcology, [3]Univ. of Arizona, Tucson, AZ; [5]Princeton Univ., Princeton, NJ; [6]Dept Pharmacol., Univ. of Arizona Col. of Pharm., Tucson, AZ

**Abstract:** The Centers for Disease Control and Prevention recommend non-opioid therapy for chronic pain. Here, we investigated the possible antinociceptive effects of several light emitting diodes (LED), in the visible spectrum, on naïve and neuropathic pain rats. Green LED (wavelength 525 nanometers) exposure for eight hours for five days increased withdrawal latency to a noxious thermal stimulus, which persisted for four days following termination of last exposure. The antinociception was mediated via actions on central mu-opioid receptor pathways unrelated to stress. No apparent side-effects were noted and motor performance was not impaired. Blocking pain-modulatory pathways by inactivation of the rostral ventromedial medulla prevented expression of light-induced antinociception. Antinociception was mediated through the visual system. Additionally, green-LED exposure reversed thermal and mechanical hyperalgesia in rats with spinal nerve ligation or injection of envelope glycoprotein 120 of HIV-1. Further work revealed that Green-LED acts additively to produce antinociception when combined with morphine. This suggests that green-LED may be opioid sparing. Given the safety profile of Green-LED, we conducted a pilot clinical trial for the management of migraine and fibromyalgia. Eight patients were divided into two groups. The first group received white-LED as a control and the second group received green-LED. The patients were blinded to the effect of Green-LED. Patients were asked to self-administer themselves green- or white-LED for 1-2 hours every night for 10 weeks. We used the Numerical Pain Scale (NPS) from 0-10 as the primary outcome measurement. Of the four patients enrolled in the control white LED, two patients quit the study for lack of any perceived benefit. The other two patients completed the study and reported 0% pain change. Patients enrolled in the Green-LED group reported on average 44.5% improvement of their fibromyalgia and migraines. This pilot study sets the stage

for an appropriately powered larger clinical trial for green light therapy as a possible adjunct for chronic pain conditions.

**Disclosures:** **M.M. Ibrahim:** None. **A. Patwardhan:** None. **K. Gillbraith:** None. **J. Hanson:** None. **A. Moutal:** None. **W. Li:** None. **S. Cai:** None. **L.A. Chew:** None. **X. Yang:** None. **A. Dorame:** None. **T.P. Malan:** None. **T.W. Vanderah:** None. **F. Porreca:** None. **R. Khanna:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.19/Y4

**Topic:** D.03. Somatosensation: Pain

**Title:** Development and characterization of an injury-free rodent model of hyperalgesia relevant to fibromyalgia syndrome

**Authors: *R. KHANNA**, A. PATWARDHAN, K. GILBRAITH, J. HANSON, A. MOUTAL, W. LI, L. CHEW, S. S. BELLAMPALLI, A. DORAME, X. YANG, P. MALAN, T. VANDERAH, F. PORRECA, M. IBRAHIM
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**Abstract:** Fibromyalgia syndrome is a common and chronic disorder characterized by widespread pain, diffuse tenderness, and a number of other symptoms including fatigue, sleep disturbances, as well as depression and anxiety. Fibromyalgia affects 5 million Americans age 18 or older. Between 80 to 90 percent of those diagnosed with fibromyalgia are women; however, men and children also can be affected. Thus, an animal model of fibromyalgia syndrome ideally should include widespread pain and associated symptoms. Here, we present a novel rat model for generalized allodynia following exposure to red light emitting diodes (LEDs). Rats exposed to red LEDs (620-630 nanometer) exhibited time- and dose-dependent diffuse thermal and mechanical hypersensitivity. The nociceptive effects of red LED were mediated through the visual system, with female rats being more sensitive to the effects of red LED. Red LED-induced generalized allodynia was reversed with some current medications used for managing fibromyalgia including gabapentin, tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors, and NSAIDs. Acetaminophen failed to reverse the red LED induced hypersensitivity. The hyperalgesic effects of the red LED were blocked when bicuculline, a GABA-A receptor antagonist, was administered into the ventromedial medulla suggesting a role for increased descending facilitation in the pain pathway. Using the elevated plus maze assay, rats exposed to red LED also exhibited increased levels of anxiety. Pharmacological and proteomic profiling of dorsal root ganglion and trigeminal root ganglion neurons from red-LED exposed rats identified significant increases in activity of voltage-gated calcium channels, with no changes in potassium

or sodium currents. Thus, we propose red LED induced hyperalgesia as an injury-free model that may allow mechanistic exploration of fibromyalgia syndrome.

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**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

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**Program#/Poster#:** 484.20/Y5

**Topic:** D.03. Somatosensation: Pain

**Support:** KIOM 17070

NRF 2015M3A9E3052338

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**Title:** Enhanced analgesic effect of rough needle surface acupuncture in rats with peripheral nociceptive stimulus

**Authors:** ***S. KWON**[1], Y. LEE[2], S.-Y. KANG[1], O. KWON[1], J.-Y. MOON[1], S. SEO[1], K.-H. CHOI[1], S. KIM[1], S. BANG[1], J. KIM[1], Y. RYU[1], H.-J. PARK[2], D.-H. HAHM[2]
[1]KM Fundamental Res. Div., Korea Inst. of Oriental Med., Daejeon, Korea, Republic of; [2]Kyung Hee Univ., Seoul, Korea, Republic of

**Abstract:** BACKGROUND: “Winding of connective tissue” induced by needle grasp force has been suggested as involving in therapeutic effectiveness of twirling-manipulated acupuncture. We sought to investigate how the frictional force on twirling needle surface affects the winding of connective tissue and acupuncture’s analgesic effect in rats with peripheral nociceptive stimulus. METHODS: To make different level of scratch on the needle surface, the needles were longitudinally rubbed with silicon carbide sandpapers of different grit numbers. The roughness of surface and rotating torque were then measured by atomic force microscope and Acusensor®, respectively. The morphological changes of connective tissue induced by twirling manipulation of acupuncture with various roughness were analyzed using hematoxylin and eosin (H-E) staining. Finally, the effects of coarse surface on anti-nociception were tested in rat tail-flick latency (TFL) and formalin test. RESULTS: The rougher surface induced the stronger needle grasp force and the thicker winding of subcutaneous connective tissue while acupuncture was twirling-manipulated. TFL was increased as the rougher surface needle was applied into the acupuncture point ST36 on rat’s tibialis muscle. In the formalin test, the rougher needle also

showed the larger analgesic effect during both early and late phases compared to non-rubbed normal needle. CONCLUSION: The rougher surface of the acupuncture needle significantly enhances anti-nociceptive effect in rats, which partially supports the mechanical signaling theory through wound connective tissue induced by twirling-manipulated acupuncture.

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**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.21/Y6

**Topic:** D.03. Somatosensation: Pain

**Support:** KIOM 17070

HI15C0007

**Title:** Median nerve stimulation of low frequency stimulator relieves pain behavior in docetaxel-induced neuropathic mice

**Authors: *S.-Y. KANG**, O. KWON, J.-Y. MOON, S. SEO, S. KWON, S. BANG, S. KIM, S. CHO, K.-H. CHOI, J. KIM, Y. RYU
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**Abstract:** Docetaxel, a chemotherapeutic agent used to treat breast cancer, produces a robust painful neuropathy signs that are aggravated by mechanical and thermal stimuli. The aims of this study were to investigate the analgesic effects of low frequency stimulator on docetaxel-induced neuropathic pain in mouse and to identify a role of median nerve. Peripheral neuropathy was induced with intraperitoneally injected docetaxel (5mg/kg) on 5 consecutive days in male ICR mouse. Low frequency stimulation (Care band, 30 Hz) was administered on top of the median nerve of the bilateral wrist. The pain behavior signs were evaluated by von Frey filaments and thermal stimulator on the hind paw, respectively. Also, we measured “50 kHz” and “22 kHz” ultrasonic vocalizations using ultrasound microphones (frequency range: 10-200 kHz, Avisoft Bioacoustics) before and after low frequency stimulation. After the mouse developed neuropathic pain behavior, a single administration of low frequency stimulator significantly attenuated docetaxel-induced mechanical allodynia and thermal hyperalgesia. In addition, treatment with docetaxel for five consecutive days selectively increased the 22 kHz ultrasonic vocalization while administration with low frequency stimulator showed a meaningful decrease. Interestingly, the amputation of bilateral median nerve completely reversed analgesic effect of

low frequency stimulator. We showed that low frequency stimulator significantly alleviated docetaxel-induced mechanical allodynia and thermal hyperalgesia in neuropathic mouse via a bilateral median nerve. Collectively, results of this study suggest that median nerve stimulation using low frequency can be a potential strategy for the management of chemotherapy induced neuropathy. Although this study might be performed in the animal model by well-designed manner, clinical study will be needed to confirm the analgesic effect of low frequency stimulator.

**Disclosures:** **S. Kang:** None. **O. Kwon:** None. **J. Moon:** None. **S. Seo:** None. **S. Kwon:** None. **S. Bang:** None. **S. Kim:** None. **S. Cho:** None. **K. Choi:** None. **J. Kim:** None. **Y. Ryu:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.22/Y7

**Topic:** D.03. Somatosensation: Pain

**Support:** CIHR

NSERC

LAEF

FRQS

**Title:** Chemogenetic Gq-linked sensitization of nociceptive pathways in freely moving rodents

**Authors: *H. ALKHANI**, A. ASE, P. A. SEGUELA
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**Abstract:** Pain is an unpleasant acute or chronic sensation experienced following peripheral injury, inflammation or ischemia. Current models used to investigate pain behaviors in rodents are plagued with pitfalls ranging from lack of spatiotemporal specificity to mandatory invasiveness. Here, we report a novel transgenic mouse model based on hM3D (Gq-coupled DREADD)-mediated sensitization of peripheral nociceptive pathways in virally-transduced Nav1.8(+) nociceptors, without administration of any external noxious stimuli or injury. Systemic activation of hM3D induced by intraperitoneal clozapine N-oxide (CNO) injections evoked strong nocifensive behavior with reduced locomotion, squinting of the eyes and ruffled fur. Intradermal paw injections of CNO resulted in robust acute thermal and mechanical sensitization as measured in Hargreaves and Von Frey tests. Moreover, CNO induced edema and redness in the injected paws, indicating the activation of neurogenic inflammatory mechanisms

similarly observed in sensitization protocols with capsaicin. The observed nocifensive behaviors appear to be specifically due to the contribution of small and medium diameter Nav1.8(+) DRG neurons, as indicated by our histology data, with fiber projections limited to the lamina I and II layers of the dorsal horn of spinal cord. These findings demonstrate for the first time the chemogenetic control of peripheral sensitization in behaving mammals and enables selective activation of the same class of afferents in vivo. Our results provide a proof-of-concept demonstration that chemogenetic interrogation of the contribution of specific classes of genetically-identified primary afferents to peripheral sensitization is possible. Non-invasive chemogenetic rodent pain models combining effective spatial penetrance with neuronal specificity have the potential to facilitate drug development and target validation for migraine or chronic pain relief.

**Disclosures: H. Alkhani:** None. **A. Ase:** None. **P.A. Seguela:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.23/Y8

**Topic:** D.03. Somatosensation: Pain

**Support:** CIHR

NSERC

LAEF

**Title:** Dopaminergic modulation of the medial prefrontal cortex: A role in chronic pain?

**Authors: *K. LANCON**, M. ZAMFIR, P. A. SEGUELA
Montreal Neurolog. Institute, McGill Univ., Montreal, QC, Canada

**Abstract:** The anterior cingulate cortex (ACC) in the medial prefrontal cortex (mPFC) has long been associated with the affective components of pain perception. Pyramidal neurons in layer 2/3 of the ACC display hyperexcitable characteristics in chronic pain. Optical silencing of these same neurons has proven to reverse neuropathy-induced hyperalgesia. Hyperpolarization-activated HCN channels, highly expressed in the mPFC, have been reported to modulate neuronal excitability. The inward currents of these cAMP-gated cation channels (Ih) control the input resistance of cells and therefore play a major role in the function of normal and pathological cortical circuits. Gs-coupled D1 dopamine receptors (D1R), localized close to HCN channels, are responsible for up regulating intracellular cAMP. Our whole cell patch clamp results indicate that D1R activation is inhibitory in layer 2/3 pyramidal cells in the ACC, hinting at a dopaminergic control on prefrontal activity in chronic pain conditions. We are in the process

of establishing the role of HCN channels as well as the molecular target in dopamine-mediated prefrontal inhibition. Furthermore, we will investigate potential analgesic effects of increasing dopamine release in the ACC in vivo in acute and chronic pain conditions. Selective optogenetically-evoked release of dopamine in the ACC has the potential to cause a D1R-mediated inhibition of layer 2/3 ACC pyramidal neurons. We plan on stimulating optically ascending ChR2+ dopaminergic projections from the ventral tegmental area (VTA) to the ACC, in hopes of producing an analgesic effect or a loss of neuropathy-induced hyperalgesia and allodynia in freely-moving mice.

**Disclosures: K. Lancon:** None. **M. Zamfir:** None. **P.A. Seguela:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.24/Y9

**Topic:** D.03. Somatosensation: Pain

**Support:** Wellcome Trust 102645

Medical Research Council MR/L003430/1

**Title:** Dynorphin- and nNOS-containing neurons in the mouse spinal dorsal horn play different roles in itch and pain mechanisms

**Authors: *E. POLGAR**[1], H. WILDNER[2], H. U. ZEILHOFER[2], A. J. TODD[1]
[1]Univ. Glasgow, Glasgow, United Kingdom; [2]Inst. of Pharmacol. and Toxicology, Univ. of Zürich, Zürich, Switzerland

**Abstract:** Chronic itch and pain are often difficult to treat and represent major unmet clinical needs. Although there has been extensive study of the neuronal circuits that process nociceptive information, interest in itch mechanisms emerged only more recently and we know less about the neuronal circuitry responsible for transmitting and modulating pruriceptive input. To understand how different types of sensory information are processed in the spinal dorsal horn we need to unravel the complex synaptic circuits involving interneurons, which form the vast majority of neurons in the superficial laminae.
Recently we identified four largely non-overlapping classes of inhibitory interneurons in laminae I-III defined by expression of specific neurochemical markers: 1) dynorphin/galanin, 2) neuronal nitric oxide synthesise (nNOS), 3) neuropeptide Y and 4) parvalbumin. We subsequently reported that the dynorphin/galanin and nNOS populations were specifically lost in mice lacking the transcription factor Bhlhb5, a model of chronic itch. This suggested a role for one or both of these populations in suppressing itch. However, a recent study reported that ablation of cells that

expressed Cre recombinase in a preprodynorphin-Cre ($Pdyn^{Cre}$) knock-in mouse prevented mechanical pain, but had no effect on itch.
In the present study we tested whether activating the dynorphin- and/or nNOS-containing neurons by DREADD technology would suppress itch and/or pain. AAV2.flex.hM3Dq-mCherry was injected into the L3-5 segments of the spinal dorsal horn in $Pdyn^{Cre}$ and $nNOS^{CreERT2}$ mouse lines. After appropriate survival times mice were randomly assigned to clozapine-N-oxide (CNO) or vehicle groups to study itch and pain behaviour. In the CNO-treated $nNOS^{CreERT2}$ mice we found an increase in mechanical and thermal pain thresholds but no significant effect on chloroquine (CQ)-evoked itch. In contrast, CNO-treated $Pdyn^{Cre}$ mice showed a significant reduction of CQ-evoked itch, but also developed mechanical allodynia.
These results suggest that among the inhibitory interneurons that are lost in the Bhlhb5 knock-out mice those that express dynorphin, but not those that express nNOS, are involved in suppressing itch. We also demonstrate that nNOS-containing neurons have an anti-nociceptive effect. The pro-nociceptive effect of CNO seen in the $Pdyn^{Cre}$ mice presumably results from activation of excitatory dynorphin-expressing cells (which were not ablated in the above-mentioned study).

**Disclosures:** **E. Polgar:** None. **H. Wildner:** None. **H.U. Zeilhofer:** None. **A.J. Todd:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.25/Y10

**Topic:** D.03. Somatosensation: Pain

**Support:** NIH Grant AR063228

**Title:** Effects of burn size on post-burn itch in mice

**Authors: *T. AKIYAMA**, K. SAKAI, K. SANDERS, G. YOSIPOVITCH
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**Abstract:** The majority of the post-burn patients suffer from chronic itch, which is often resistant to antihistamine treatment. Patients with larger burn surface areas exhibit more severe itch. Post-burn itch involves sensitization of itch-signaling pathways, leading to ongoing itch and alloknesis (touch-evoked itch), but the underlying mechanisms behind post-burn itch are largely unknown. We presently investigated if different sizes of scald burn affect the time course of post-burn itch in mice. We further tested whether a histamine H1R antagonist inhibits post-burn itch in mice. Moreover, we investigated if the density of intraepidermal fibers is altered in the scald burn model. A scald burn injury (7 mm or 10 mm diameter) was produced in adult C57BL/6 mice by exposing the shaved back skin to boiling water. To assess spontaneous

scratching, mice were videotaped on Days 0, 1, 3, 5, 7, 10, 14, 21, and 28 after the scald burn treatment. The 7 mm scald burn caused a transient increase in spontaneous scratch bouts that declined within 14 days. The 10 mm scald burn caused two phases of post-burn itch. Counts of spontaneous scratch bouts increased transiently on Days 1, 3, and Day 5 compared to Day 0, returned to the basal level by Day 10, and reincreased significantly on Days 14, 21, and 28. To test for alloknesis, a weak von Frey filament (VF; 0.7 mN) was repeatedly applied to post-burn skin on Days 0, 1, 3, 5, 7, 14, 21, and 28 after the scald burn treatment, and the presence or absence of evoked hindlimb scratch bouts was noted (VF stimulation does not elicit any response in naïve C57BL/6 mice). VF-evoked scratching increased significantly on Days 1 and 3, and Days 21 and 28 in the 7 mm and 10 mm scald burn model, respectively. The histamine H1 receptor antagonist chlorpheniramine was tested on Day 22 but did not inhibit spontaneous scratching or alloknesis, suggesting that non-histaminergic itch pathways are involved in post-burn itch. To investigate the density of intraepidermal fibers, the skin sections were immunostained with Protein Gene Product 9.5 antibody. Reduction of epidermal nerve fiber density was observed in the 10 mm scald burn model on Day 28. The reduction of epidermal nerve fiber density may contribute to post-burn itch through disinhibition of itch (reduction of pain signals). This new animal model appears to be useful for investigations of post-burn itch and sensitization of itch-signaling pathways.

**Disclosures:** **T. Akiyama:** None. **K. Sakai:** None. **K. Sanders:** None. **G. Yosipovitch:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.26/Y11

**Topic:** D.03. Somatosensation: Pain

**Support:** MOST 106-2321-B-002-017

**Title:** Visualize nociceptor changes in neuropathic mice with chronic constriction injury

**Authors: Y.-W. WU**, *C.-T. YEN
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**Abstract:** Neuropathic pain is caused by injury of the somatosensory nervous system. In this study we aim to use in vivo and ex vivo microscopic methods to examine the change in nociceptors under the paw skin after chronic constriction injury (CCI) of the sciatic nerve, a commonly used animal model for neuropathic pain research. Our basic hypothesis is that direct microscopic observation of free nerve endings of the nociceptors in situ and en bloc will reveal the life history of the development and maintenance of the neuropathic pain. We used genetically modified mice that intrinsically express the fluorophore tdTomato tagged to a small fiber marker,

the Nav1.8 molecule. A battery of behavior tests including von Frey hair stimulation, hot/cold plate test, acetone drop test were applied to the hind paws of the mice to test their sensitivity to mechanical, heat and cold stimuli, respectively. Ex vivo confocal microscopic and in vivo longitudinal two-photon fluorescent microscopic observation of dynamic changes of nerve plexus and free nerve endings in the hind paw were performed first before and then 2 to 21 days after CCI of the sciatic nerve. Using behavioral tests we validated mechanical and thermal hyperalgesia of the CCI mice. Combining ex vivo and in vivo microscopic observations we found the density of the Nav1.8-tdTomato nerve ending in the hind paw can be a useful biomarker for the severity of the neuropathy.

**Disclosures: Y. Wu:** None. **C. Yen:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.27/Y12

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

**Support:** CHOP Neonatology Fellows Research Grant

Battaglia Endowed Chair

**Title:** Effects of early noxious stimulation and early systemic infection on response to painful stimuli in Long-Evans hooded rats

**Authors: *C. GOMES**[1], G. A. BARR[2]
[1]Neonatology, The Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Anesthesiol. and CCM, Children's Hosp. of Philadelphia, Philadelphia, PA

**Abstract:** Painful procedural interventions are necessary in neonatal intensive care, but our knowledge of the long-term effects of these interventions is limited. Establishing a causal relationship between early painful experiences and altered responses to pain long-term remains difficult because human infants experience many confounding medical complications throughout their NICU course. Early systemic infections, for example, are commonly encountered in preterm infants but their effects on the pain response in both infancy and adulthood are unknown. The main goals of our research are to understand how painful experiences occurring early in life influence future responses to pain and how early systemic infection alters these responses. Rat pups were injected subcutaneously with either PBS or $0.1x10^6$ CFU of E-coli (ATCC 15746) suspended in PBS on post-natal day 2 (PNd2). On PNd3, pups had their left hind paw injected with 0.25% carrageenan. A separate group of pups were similarly handled but received no injection. Behavioral testing occurred at one of three specified time points: PNd8, PNd15 or after

PNd65 (corresponding with humans at full term, mid-infancy, and young adulthood, respectively). Standard pain assessments performed included plantar heat latency testing to measure basal pain levels, formalin testing to measure the acute inflammatory pain response following reinjury, and condition place aversion testing (CPA) to determine if rats develop a learned aversion to the testing chamber where they were conditioned with a painful stimulus. After behavioral testing, animals were sacrificed and brain tissue was harvested for assessment of c-fos expression as a marker of neural activation. There were no significant differences in thermal pain thresholds in carrageenan exposed pups vs. controls at any age. Early infection with E-coli did not alter this. Upon reinjury with formalin, there were no significant differences in pain response in the carrageenan vs. control group at any age. However, infection significantly increased pain scores following reinjury on both PNd8 and PNd15, but not in adults. Early systemic infection with E-coli did increase learned aversions to painful stimulation in late-infancy that persisted into adulthood, where there was a trend for infant carrageenan treatment augmenting the learned aversion. Thus, early systemic infection augments both pain and pain affect both pre-weaning and in adults.

**Disclosures: C. Gomes:** None. **G.A. Barr:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.28/Y13

**Topic:** B.09. Physiological Properties of Neurons

**Title:** Using iPSC-derived noiceptor neurons from familial dysautonomia patients to study pain physiology

**Authors: *Y. SAPIR**, J. KOH, B. WAINGER
Massachusetts Gen. Hosp., Boston, MA

**Abstract:** Familial Dysautonomia (FD) is an autosomal recessive disease characterized by broad symptoms of sensory and autonomic dysfunction. FD is caused by a single mutation in intron 20 in the *IKBKAP* gene, leading to a tissue-specific splicing defect and decreased level of wild-type IKAP protein. The disease affects the development and survival of sensory, sympathetic and some parasympathetic neurons. The main sensory manifestations in FD patients are impaired temperature and pain perceptions which involve primarily nociceptive functions, in addition to the characteristic profound dysautonomia. The ability to use nociceptors derived from FD patient induced pluripotent stem cells (iPSCs) has already served as a powerful tool to model the deficiency in FD *in vitro* and validate candidate treatments. Here, we derive nociceptor neurons from FD patient iPSCs and investigate nociceptor function on the physiological level using calcium imaging and whole-cell patch clamp. We assess the response to typical nociceptor

activators, including an assortment of transient receptor potential (Trp) channel ligands, as well the basic excitability profile of the neurons, including rheobase and action potential firing properties. The results suggest a picture of distinct physiological dysfunction as part of the FD disease process.

**Disclosures: Y. Sapir:** None. **J. Koh:** None. **B. Wainger:** None.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.29/Y14

**Topic:** D.03. Somatosensation: Pain

**Title:** Generation of patient-derived sensory neurons using iPSCs & smNPCs obtained from patients with Fabry disease

**Authors: T. KLEIN**[1], K. GÜNTHER[2], C. L. SOMMER[1], F. EDENHOFER[2], *N. ÜÇEYLER[1]
[1]Dept. of Neurol., [2]Inst. of Anat., Univ. of Würzburg, Würzburg, Germany

**Abstract: Background & Objective:** Fabry disease (FD) is an X-linked lysosomal storage disorder that particularly affects heart, kidneys, & the nervous system. Due to deficiency of the alpha-galactosidase A (GLA), the glycolipid globotriaosylceramide 3 accumulates in cells, including human dermal fibroblasts (HDFs). The major neurological symptom in FD is acral burning pain, which manifests as episodic pain like attacks & crises, or as permanent pain. The pathophysiology of FD pain is unknown & research is hindered by the lack of suitable biomaterial. Using patient-derived HDFs, our aim was to generate induced pluripotent stem cells (iPSCs), followed by the derivation of small molecules neural precursor cells (smNPCs) & subsequently differentiate these into nociceptors. Such a disease model would help to elucidate underlying mechanisms of pain pathophysiology in FD.
**Methods:** A six-mm skin punch biopsy was taken from the lateral lower leg of two female FD patients with a mutation of the *GLA* gene (patient 1: 25 years, missense mutation; patient 2: 50 years, nonsense mutation). HDFs were isolated & reprogrammed to iPSCs using a transgene-free synthetic mRNA approach. smNPCs were then derived from iPSCs, by means of dual-SMAD inhibition in suspension culture & use of chemically defined medium. smNPCs were differentiated to nociceptors using a combination of three inhibitors to promote sensory lineage commitment. Expression of pluripotency & NPC marker proteins were analyzed using immunocytochemistry (ICC). iPSC clones were characterized using fluorescence activated cell sorting & differentiation into all three germ layers.
**Results:** We generated two iPSC lines from patient 1 & three lines from patient 2. All lines displayed strong immunoreaction against established pluripotency markers. Furthermore, >98% of the cells from all three lines from patient 2 expressed TRA-1-60, & SSEA4. Embryoid body

formation was performed for one clone from patient 2 with subsequent ICC proving the presence of all three germ layers. smNPCs were generated from one clone of each patient & all showed expression of the NPC marker proteins SOX1, SOX2, Nestin, & PAX6. Differentiations showed neuronal outgrowth, with cells being positive for the neuronal marker TUJ1 & the peripheral marker peripherin.
**Conclusions:** We successfully generated iPSCs & smNPCs of FD patients using synthetic mRNA & were able to differentiate these to neurons. Upon completion of histological, molecular, & electrophysiological characterization, we will provide functional neurons as the basis of a novel *in vitro* model for mechanism-based research on FD pain pathophysiology.

**Disclosures: T. Klein:** None. **K. Günther:** None. **C.L. Sommer:** 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.; Sanofi Genzyme. **F. Edenhofer:** None. **N. Üçeyler:** 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.; Sanofi Genzyme, Shire.

**Poster**

**484. Pain Models: Physiology and Behavior I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 484.30/Y15

**Topic:** D.03. Somatosensation: Pain

**Support:** R01GM101218

R01DK103901

**Title:** The antimicrobial peptide hBD2 promotes itch through Toll-like receptor 4 signaling in mice

**Authors: J. FENG**[1], J. LUO[1], M. R. MACK[2], P. YANG[1], X. GONG[3], F. ZHANG[3], G. WANG[3], T. CAI[4], Z. MEI[3], B. S. KIM[2], S. YIN[3], *H. HU[1], *H. HU[1]
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**Abstract:** Psoriasis is one of the most prevalent chronic skin diseases associated with intense itching although the cellular and molecular mechanism of pruritus in psoriasis remains unclear. Many cytokines are selectively up-regulated in psoriasis and become candidate molecules for psoriatic itch. Human beta-defensin 2 (hBD2) is the most up-regulated member of cytokines in

the epidermis and considered as a biomarker of disease activity. However, the role of hBD2 in the genesis of itching is not understood. Here we show that hBD2 elicited a dose-dependent scratching behavior in mice. Interestingly, the hBD2-elicited scratching response was severely reduced by genetic ablation of TRPV1 function although hBD2 did not directly activate TRPV1, suggesting hBD2 activates upstream targets to release TRPV1-sensitive endogenous pruritogens to initiate itch sensation in mice. Although the putative hBD2 receptors C-C chemokine receptor type 2 (CCR2) and 6 (CCR6) are abundantly expressed by skin-resident cells, the hBD2-elicited itching was not affected by genetic ablation of either CCR2 or CCR6 function. Surprisingly, the hBD2-elicited scratching response was substantially reduced in global knockouts or myeloid cell-specific knockouts of the Toll-like receptor (TLR4) that is primarily expressed by $CD11b^{+}/CD11c^{-}$ dermal macrophages. Our findings suggest that hBD2 could act as a potent endogenous pruritogen acting on cutaneous innate immune cells through TLR4 signaling to promote TRPV1-dependent itch sensation, which expands the roles of the antimicrobial beta-defensin family and may also provide new therapeutic targets against psoriatic itch.

**Disclosures:** **J. Feng:** None. **J. Luo:** None. **M.R. Mack:** None. **P. Yang:** None. **X. Gong:** None. **F. Zhang:** None. **G. Wang:** None. **T. Cai:** None. **Z. Mei:** None. **B.S. Kim:** None. **S. Yin:** None. **H. Hu:** None. **H. Hu:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.01/Y16

**Topic:** D.03. Somatosensation: Pain

**Title:** Gait analysis in mouse mouse models of chronic widespread pain

**Authors: *C.-H. LEE**[1], S.-Y. HSIEH[2], T.-H. HSIEH[3], C.-C. CHEN[4]
[1]Inst. of Biomed. Sci. Academia Sinica, Taipei, Taiwan; [2]Dept. of Biochem. Sci. and Technol., Natl. Taiwan Univ., Taipei, Taiwan; [3]Dept. of Physical Therapy and Grad. Inst. of Rehabil. Sci., Chang Gung Univ., Taoyuan, Taiwan; [4]Academia Sinica, Taipei, Taiwan

**Abstract:** Chronic widespread pain is quite unbearable and affecting quality of life in patients but is often difficult to treat. In preclinical studies, many drugs with high efficacy on evoke-pain monitoring platforms (e.g., von Frey and/or hot plate tests) were often failed in clinical trial. Thus, besides evoked pain assessment, methods to evaluate non-evoked pain (e.g., spontaneous pain) responses are urged in preclinical studies. Previous reports have demonstrated gait analysis is a useful method to evaluate spontaneous pain in mouse models of acute pain. However, whether it is still not known whether gait analysis has good sensitivity to chronic pain assessment, especially for chronic widespread pain in mouse. We analyzed mouse gait after treatment of intermittent cold stress (ICS), an animal model of fibromyalgia, which causes

mouse wide spread pain. After ICS treatment, mice developed chronic mechanical hypersensitivity at both hind paws and gastrocnemius muscle. We analyzed temporal and special parameters of mouse gait including Stance time (ST), Swing phase time (SWP), Double support time (DS), Walking speed (WS), Step length (StepL), Stride length (StrideL), Base of support (StepW), Print length (PL), Foot angle (FtAng), Intermediary toe spread (ITS) and Toe spread (TS). As compared with naïve mice, ICS-treated mice significantly decreased scores in ST, DS, PL and increased scores in StepW. Interestingly, the StepW parameters of ICS mice could be corrected after intraperitoneally injection of pregabalin, a well-known analgesic drug for fibromyalgia. Taken together, gait analysis might be useful for detecting chronic widespread pain behavior in mice.

**Disclosures: C. Lee:** None. **S. Hsieh:** None. **T. Hsieh:** None. **C. Chen:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

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**Program#/Poster#:** 485.02/Y17

**Topic:** D.03. Somatosensation: Pain

**Support:** NIH Grant P031B141014

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**Title:** Selective activation of membrane estrogen receptors rapidly attenuates opioid receptor-like 1 receptor-mediated suppression of nerve injury-induced tactile hypersensitivity possibly via GIRK channel modulation

**Authors: *D. M. HECKARD**[1], S. NAG[2], C. D. WEAVER[4], S. S. MOKHA[3]
[1]Meharry Med. Col., Nashville, TN; [2]Neurosci. and Pharmacol., [3]Meharry Med. College, Dept of Neurosci. and Pharmacol., Nashville, TN; [4]Pharmacol., Vanderbilt Univ., Nashville, TN

**Abstract:** Numerous studies have reported that women have a higher prevalence of chronic pain disorders than men. We have previously shown that estrogen attenuates opioid receptor like -1 (ORL1) receptor mediated thermal antinociception in females [Claiborne et al. J Neurosci. 26:13048-53, 2006]; and down-regulates the ORL1 gene expression [Flores et al. Neurosci. 118:769-78, 2003]. Recently, we have demonstrated that activation of membrane estrogen receptors (GPR30, Gq-mer, ER α, but not ER β) rapidly abolishes ORL1-mediated acute thermal antinociception via an ERK2-dependent non-genomic mechanism [Small et al. Neurosci. 255:177-190, 2013]. However, the effect of membrane estrogen receptors (mERs) on ORL1-mediated attenuation of neuropathic pain and the underlying mechanisms remain unknown. Thus, the present study investigated whether selective activation of mERs attenuates ORL1-

mediated suppression of nerve injury-induced tactile hypersensitivity. The spared nerve injury (SNI) model as previously described by Decosterd and Woolf [Pain. 87:149-58, 2000] was employed to induce mechanical hypersensitivity in male and OVX female Sprague Dawley rats. After a 7-day recovery period, sham and SNI rats were intrathecally administered a selective mER agonist immediately followed by OFQ, the endogenous ligand for the ORL1 receptor, into the lumbosacral spinal cord of rats through an implanted PE-10 cannula. Paw withdrawal thresholds (PWTs) were recorded using an automated dynamic plantar aesthesiometer. A thallium flux assay [Weaver et al. J Biomol. Screen. 9(8);2004] was also utilized in HEK cells transfected with GIRK I,II channels, ORL1 and mERs to determine the rapid effect of mER activation on ORL1-mediated thallium flux. SNI significantly reduced PWTs in both males and OVX females. Intrathecal administration of OFQ significantly increased PWTs in both males and OVX females while selective mER activation rapidly abolished (within two minutes) OFQ-induced increase in PWTs. Further, preliminary data suggest an increase in thallium flux following OFQ application, which seems to be reduced by pretreatment with mER agonist. Thus, we conclude that activation of mERs rapidly attenuates ORL1-mediated suppression of nerve injury-induced tactile hypersensitivity possibly via decreasing the GIRK channel function. This work provides evidence of a biological mechanism that may underlie female vulnerability to the development of chronic pain disorders.

**Disclosures: D.M. Heckard:** None. **S. Nag:** None. **C.D. Weaver:** None. **S.S. Mokha:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

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**Program#/Poster#:** 485.03/Y18

**Topic:** D.03. Somatosensation: Pain

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MOST 106-2321-B-010-009-

MOST 103-2320-B-010-041-MY3

MOST 105-2321-B-010-012

**Title:** Chemogenetic interrogation of anxiety- and depression-like behaviors in a mouse model of fibromyalgia

**Authors: *W.-Y. WONG**[1], C.-C. LIEN[1,2]
[1]Inst. of Neuroscience, Natl. Yang-Ming Univ., Taipei, Taiwan; [2]Brain Res. Center, Natl. Yang-Ming Univ., Taipei, Taiwan

**Abstract:** Fibromyalgia (FM) is a chronic pain disorder, which is considered to be a chronic "centralized" pain state underpinned by aberrant neurotransmissions and brain excitability. Clinical studies show that patients of FM often suffer from psychiatric disorders such as anxiety and depression. However, little is known about circuit mechanisms underlying comorbid pain and emotional disorders. Our preliminary study found that the phosphorylated ERK (pERK) level increased in the lateral subdivision of central amygdala (CeL) in a FM-like mouse model, so called acid-induced muscle pain model. The amygdala is not only a key structure for emotions but also serves a major receiver of purely nociceptive signals. In this study, we assumed that modulation of CeL activity could ameliorate comorbid pain and emotional disorders. The CeL consists of two types of neurons: somatostatin-expressing ($SOM^+$) and non-somatostatin-expressing ($SOM^-$) neurons. We found that silencing of $SOM^+$ neurons in the FM-like mouse model using inhibitory designer receptors exclusively activated by designer drugs (DREADDs) resulted in a significant decrease in mechanical hypersensitivity in both hindpaws of the FM-like mouse model after intraperitoneal injection of clozapine-N-oxide, a ligand for DREADD receptors. Furthermore, anxiety- and depression-like behaviors in the FM-like mouse model were significantly reversed after silencing $SOM^+$ neurons. Our findings suggest that the CeL might be a therapeutic target for chronic pain and associated mood disorders.

**Disclosures: W. Wong:** None. **C. Lien:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.04/Z1

**Topic:** D.03. Somatosensation: Pain

**Support:** NIDCR grant DE022129

**Title:** Meal pattern differences between mid- and late-pregnant rats after CFA-induced temporomandibular joint (TMJ) nociception

**Authors: *M. UMORIN**, P. KRAMER, L. BELLINGER
Biomed. Sci., Texas A&M Univ. Col. of Dent., Dallas, TX

**Abstract:** Women often report having fewer TMJ symptoms during pregnancy.
Thus, our study aimed at answering the question: does TMJ nociception, as measured by a behavioral assay differ during pregnancy, potentially due to the effect of sex steroids? We have shown that meal pattern analysis including rate, duration, and frequency can be used to measure orofacial nociception. In rats, the estradiol concentrations commonly observed during pregnancy vary from 10 pg/mL (mid pregnancy) to 60 pg/mL (late pregnancy).
In these experiments, 32 Sprague-Dawley rats were randomly allocated to either mid (E11)- or

late (E18) pregnancy groups. The animals within each group were further allocated to a saline or CFA treatment. At E11 or E18, the animals were injected bilaterally into TMJ with either saline (10 µL) or 1 µg/µL CFA (10 µL). Nociception was measured with a feeding assay (pellet recording) and analyzed by comparing intra-meal rates using a distance-based permutation method.
While aggregate statistics showed very little differences between groups, the intra-meal rate analysis revealed differences between the saline and CFA groups for both mid-and late-stage pregnant rats. Furthermore, comparison of intra-meal rates indicated that CFA-injected rats in the mid-pregnant group would start meals at half the rate of the control group and would continue eating a meal for almost twice as long suggesting a greater nociceptive response in this mid-pregnancy group. CFA-injected rats in late-pregnant group would start at the same rate as the control group but would continue eating for longer periods compared to the corresponding controls. The observed differences may be due to different plasma concentrations of estradiol that were observed in the mid-and late-pregnant rats.
This is the first time the intra-meal patterns were used to study TMJ nociception in pregnant rats. Thus, we conclude that one potential reason women report fewer TMJ symptoms during pregnancy is the higher level of circulating sex hormones.

**Disclosures:** **M. Umorin:** None. **P. Kramer:** None. **L. Bellinger:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.05/Z2

**Topic:** D.03. Somatosensation: Pain

**Title:** The role of astrocyte elevated gene-1 in mouse models of inflammatory and neuropathic pain

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**Abstract:** Astrocyte elevated gene-1 (AEG-1), also known as metadherin or LYRIC, is a novel human immunodeficiency virus-1 and tumor necrosis factor-α inducible oncogene. AEG-1 mRNA is ubiquitously expressed in all normal tissues. However, the physiological function of AEG-1 is not well known. It has been shown that enhanced angiogenesis and inflammation upregulates AEG-1. In addition, AEG1 is one of the modulators of HIV-1-associated neuroinflammation. AEG-1 activates NF-κB and NF-κB is a key regulator of pro-inflammatory cytokines, which suggest a potential role of AEG-1 in the inflammatory processes.
We aimed to determine whether AEG-1 influences the development of inflammatory and neuropathic pain behavior in mouse models of complete Freund's adjuvant (CFA)-induced

inflammatory pain and chronic constriction nerve injury (CCI)-induced neuropathic pain in the presence (WT mice) and absence (KO mice) of AEG-1. Our hypothesis was that AEG1 inhibition will reverse the initiation and maintenance of inflammation and pain.
The results showed that hyperalgesic and allodynic response to CFA injections were reduced in male and female AEG-1 KO mice. However, both hyperalgesia and allodynia observed in the CCI model were similar in AEG-1 WT and KO mice. Interestingly, the antiallodynic properties of gabapentin and morphine in CCI model were enhanced in AEG-1 KO mice compared with WT mice.
In summary, our results highlight the involvement of the AEG-1 in development inflammatory pain but not neuropathic pain. Morphine and gabapentin have higher potency in AEG-1 KO mice. Our results indicate an important modulatory role of AEG-1 in chronic inflammatory pain.

**Disclosures: D. Bagdas:** None. **M. Carper:** None. **D. Sarkar:** None. **M. Damaj:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.06/Z3

**Topic:** D.03. Somatosensation: Pain

**Support:** MOST Grant

NHRI Grant

**Title:** Effects of oxaliplatin on the development of neuropathy and cognitive impairment in the mouse

**Authors: *L.-H. CHEN**[1], Y.-F. CHEN[1], H.-C. HAN[2], M.-R. SHEN[1]
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**Abstract:** Oxaliplatin treatment, a platinum-based chemotherapy used to treat colorectal cancer, is afflicted by prominent dose-limiting neurotoxicity. About 20% patients receiving oxaliplatin with a cumulative dose of 850 mg/m$^2$ have been reported with severe, partially irreversible sensory or motor neuropathy. In the clinical practice, patients receiving oxaliplatin also often experience changes in mood and cognitive function. Consequently, the present study was designed to develop a mouse model of oxaliplatin-induced cognitive deficit and affective symptoms to identify treatment strategies and their underlying mechanisms of action. Intraperitoneal injections of oxaliplatin (3 mg/kg, 5 consecutive days for 2 cycles) resulted in the development and maintenance of mechanical and cold allodynia. Oxaliplatin-treated mice displayed cognitive impairment as measured by novel object recognition, Y-maze alteration and

Y-maze recognition test. In addition, oxaliplatin also induced depression-like behavior, as assessed in the forced swim test, tail suspension and sucrose preference test. Taken together, oxaliplatin showed significant impacts on nociception, cognition, affective states in C57BL/6J mice. The characterization of this murine model of chemotherapy-induced neuropathic pain and cognitive impairment provides the basis for determining the mechanisms underlying severe adverse effects elicited by oxaliplatin.

**Disclosures: L. Chen:** None. **Y. Chen:** None. **H. Han:** None. **M. Shen:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.07/Z4

**Topic:** D.03. Somatosensation: Pain

**Title:** Hypersensitivity to acute pain in a mouse model of early blindness

**Authors: *S. TOUJ**[1], S. ALAIN[2], G. BRONCHTI[3], M. PICHE[4]
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**Abstract:** Early blindness results in anatomical, functional and behavioral changes in human and animals. Recently, the nociceptive system of congenital blind individuals was investigated and it was reported that they have lower heat pain thresholds. The aim of the present study was twofold. Firstly, we aimed at developing a mouse strain from which half of individuals are born sighted with normal eyes (heterozygous) and half are born anophthalmic (homozygous). The so-called ZRDBA mouse was obtained through genetically controlled crossing between ZRDCT eyeless mice and DBA eyed mice. This unique strain allows studying the impacts of early blindness on sensory functions without the potential confound of strain differences. Secondly, we aimed at investigating the behavioral response to acute pain in this model of blindness. A total of 40 mice were used, including 20 anophthalmic and 20 sighted mice, with each group comprising 10 males and 10 females. All experimental procedures were approved by the animal care committee of “Université du Québec à Trois-Rivières”, in accordance with the guidelines of the Canadian Council on Animal Care and the guidelines of the Committee for Research and Ethical Issues of the International Association for the Study of Pain (IASP).To assess the response to acute pain, the formaline test was performed by injecting 20 $\mu l$ of a formaline solution (2.5% v/v in saline) subcutaneously, into the right dorsal hindpaw. Mice were observed for a total of 45 minutes and the number of hindpaw licking events was calculated for every 5-minute interval. Formalin injection induces pain with an early acute phase lasting around 10 minutes and an inflammatory phase beginning 20 minutes after the injection and lasting around 10 minutes. Pain

sensitivity was different between phases and was affected by blindness (PHASE x GROUP interaction: $F_{1,36} = 7.4$, $p = 0.01$; $\eta p = 0.17$) and marginally by sex (PHASE x SEX interaction: $F_{1,36} = 3.7$, $p = 0.06$; $\eta_p = 0.09$). Planned contrasts revealed that during the acute phase, blind mice were more sensitive to pain compared with controls for both sexes combined ($p = 0.006$), although the effect was significant in females ($p = 0.03$) but not in males ($p = 0.07$). In the inflammatory phase, no difference was observed between groups, either in females or males or for both sexes combined (all p's > 0.3). Consistent with human studies, these results indicate that blindness is associated with pain hypersensitivity. Future anatomical and functional studies are needed to determine the underlying mechanisms of this pain hypersensitivity.

**Disclosures: S. Touj:** None. **S. Alain:** None. **G. Bronchti:** None. **M. Piche:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.08/Z5

**Topic:** D.03. Somatosensation: Pain

**Title:** Involvement of HMGB1 in postoperative pain

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**Abstract:** Severe pain accompanying histological damage and inflammation after surgical invasion may continue for several days. Since the relief of postoperative pain is extremely important to avoid complications and improve QOL, it is necessary to develop more effective therapeutic drugs on the basis of the molecular mechanisms for postoperative pain. High mobility group box 1 (HMGB1), a nuclear protein, is passively released from necrotic cells and actively secreted by certain cells including activated macrophages (Mφ). Given our evidence for the involvement of HMGB1 in inflammatory hyperalgesia, chemotherapy-induced neuropathic pain and visceral pain following cystitis or pancreatitis, we examined whether HMGB1 contributes to the development or maintenance of postoperative pain induced by hindpaw plantar incision in mice. The surgery caused significant decrease in nociceptive threshold within 2 h, as assessed by von Frey test, and the mechanical allodynia lasted for 48 h. The anti-HMGB1-neutralizing antibody (Ab) or recombinant human soluble thrombomodulin (TMα), capable of inactivating HMGB1, when administered i.p. 1 or 24 h after the surgery, transiently restored the postoperative allodynia. Pretreatment with Ab or TMα slightly delayed the development of the postoperative allodynia. Any of antagonists of receptor for advanced glycation end-products (RAGE), Toll-like receptor 4 (TLR4) and CXC chemokine receptor 4 (CXCR4), known as

pronociceptive targets for HMGB1, reversed the postoperative decrease in nociceptive threshold. Preadministration of ethyl pyruvate, known to inhibit the release of HMGB1 from Mφ, or minocycline, a Mφ/microglia inhibitor, did not affect the postoperative allodynia. Plasma HMGB1 levels did not change after the surgery. On the other hand, the protein levels of HMGB1, but not RAGE, TLR4 and CXCR4, decreased in the dorsal root ganglion and increased in the sciatic nerves 1 day after the surgery. Together, HMGB1 derived from the cells other than Mφ is considered to participate in postoperative pain by activating RAGE, TLR4 and CXCR4.

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

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.09/Z6

**Topic:** D.03. Somatosensation: Pain

**Support:** Project CONACyT 178027

SIP 20171838

Arroyo-Lira Arlette is a CONACyT fellow (Grant number 269377)

**Title:** Evaluation of cannabinoid, opioid and serotoninergic receptors on the antinociceptive effect of peripheral administration of docosahexaenoic acid (DHA)

**Authors: *A. G. ARROYO LIRA**, A. E. CHÁVEZ-PIÑA
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**Abstract: Introduction:** Pain is the oldest medical problem and has been a challenge for physicians since the origin of humanity and remains as a global public health issue. Pain relief can be achieved by a diversity of methods, with drug use being the basis of analgesic treatment but the adverse effects caused by analgesics limit their use. As part of endogenous pain perception and modulation has been involved cannabinoid, opioid and serotoninergic agonist and their receptors. Docosahexaenoic acid (DHA) is an omega-3 fatty acid. Even though its antinociceptive effect has been demonstrated, the mechanisms still not well-defined. Based on the above consideration the aim of his work was to evaluate the participation of cannabinoid, opioid and serotoninergic receptors on the antinociceptive effect of peripheral administration of docosahexaenoic acid (DHA). **Methods:** Female Wistar rats were administered with DHA (562

µg/paw) 75 min before the formalin (1%) injection and percentage of antinociception was calculated. In the same way, the antinociceptive mechanisms of DHA was evaluated using specific antagonist for cannabinoid (rimonabant; 30-100 µg/paw), opioid (naloxone; 50-100 µg/paw) and serotoninergic (methiothepin; 100-177.82 µg/paw) receptors. **Results:** Administration of DHA induced an antinociceptive effect (46.41 ± 3.92 %). Rimonabant administration reduces DHA´s antinociceptive effect in a dose dependent fashion, abolishing the antinociceptive effect of DHA when 100 µg/paw was administered. Naloxone administration attenuated DHA-induced antinociception. Finally, methiothepin administration did not modify the antinociceptive effect of DHA. **Conclusions:** Our results suggest that DHA produces antinociception *via* cannabinoid and opioid receptors located at peripheral sites in the rat formalin test. **Acknowledgments:** The authors acknowledge the support provided by the National Council for Science and Technology (Project CONACyT 178027) and SIP 20171838. Arroyo-Lira Arlette Guadalupe is a CONACyT fellow (Grant Number 269377).

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**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.10/Z7

**Topic:** D.03. Somatosensation: Pain

**Support:** Rita Allen Foundation

**Title:** The SAD weekend: A perilous north american tradition

**Authors: *S. K. TOTSCH**, *S. K. TOTSCH, S. A. LOPEZ, T. L. QUINN, R. Y. MEIR, R. E. SORGE
Psychology, Univ. of Alabama At Birmingham, Birmingham, AL

**Abstract:** Obesity and chronic pain often co-occur. It is known that poor quality diet and/or obesity contribute to a chronic inflammatory state that may lead to susceptibility to chronic pain. Previously, we developed a Standard American Diet (SAD) and an Anti-inflammatory Diet (AID) to investigate the effects of diet on pain. The SAD is high in refined sugar, carbohydrates, trans and saturated fatty acids. The AID includes omega-3 fatty acids, green tea extract, sulforaphane, resveratrol, curcumin, and ginseng; all known to have anti-inflammatory properties. In the current study, we were interested in the impact of unhealthy weekend binges on pain and recovery from inflammatory injury. Male and female mice were fed a SAD, AID or regular (REG) chow diet for 14 weeks Monday to Friday. On Saturday and Sunday, subsets of animals from the AID or REG groups were switched to the SAD diet, to model weekend eating habits. Mechanical sensitivity and body weight were assessed weekly whereas glucose tolerance

was assessed at weeks 8 and 16. Microbiome analysis was performed at week 14. At this time after 14 weeks of diet consumption, chronic pain was induced through intraplantar injection of complete Freund's adjuvant (CFA). Following CFA injection, the SAD-fed mice showed prolonged recovery while the AID-fed mice had shortened recovery time. Interestingly, animals that were switched to the SAD on weekends had further protracted recovery, comparable to animals who solely consumed the SAD. Of clinical interest, animals that solely consumed the SAD had a greater proportion of proteobacteria and less bacteroidetes, while animals that solely consumed the AID had greater proportion of actinobacteria and less proteobacteria. Animals that switched between diets had a mixture of the two. These data suggest that short-term, repeated consumption of the SAD has similar detrimental effects to sole SAD consumption. However, consuming AID during the week remains beneficial in terms of gut microbiota. Work is currently underway using flow cytometry to determine the impact of the diets on T cell infiltration into the spinal cord.

**Disclosures: S.K. Totsch:** None. **S.A. Lopez:** None. **T.L. Quinn:** None. **R.Y. Meir:** None. **R.E. Sorge:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.11/Z8

**Topic:** D.03. Somatosensation: Pain

**Title:** The impact of inflammatory pain on decision-making

**Authors: *C. A. SALCIDO**, M. K. GELTMEIER, P. N. FUCHS
Univ. of Texas At Arlington, Arlington, TX

**Abstract:** Clinical assessments using the Iowa Gambling Task reveal that pain negatively affects decision-making processes and leads to risky decisions. Despite the gains made in elucidating the cognitive component of pain, the neurobiological factors of how pain alters decision-making is not clear. Therefore, we examined the impact of inflammatory pain and morphine on decision-making processing. Sprague Dawley rats were trained using a rodent version of the Iowa Gambling Task (RGT). Animals were administered a s.c. injection of Complete Freund's Adjuvant (CFA) or saline to induce an inflammatory condition. Thirty minutes after, animals were administered morphine (3 mg/kg) or saline. Thirty minutes later, animals were tested using the RGT. Percent of best choice and percent omissions in the RGT were used to assess cognitive performance. After the RGT, animals were subjected to the Place Escape/Avoidance Paradigm (PEAP) to measure the affective response to CFA. On day ten, animals were given the same drug injection as test day and then thirty minutes later, were tested using RGT and PEAP paradigms. RGT data revealed no differences in best choice regardless of pain, drug, or time conditions.

However, morphine treatment significantly increased percent of omissions versus saline. PEAP results revealed a significant increase in avoidance behavior for CFA animals on days one and ten of testing. The escape/avoidance response was reduced in morphine treated animals. In conclusion, specific patterns of decreased cognitive performance in decision-making were not apparent for the CFA inflammatory condition. There was significant escape/avoidance indicating robust pain affect. The findings of significant pain affect, but lack of impaired cognitive functioning highlights a possible separation of pain affect/motivation from evaluative/cognitive component. Future studies will further assess the multidimensionality of pain and cognition in order to obtain a comprehensive understanding of pain behaviors. Such approaches can provide critical information that will ultimately translate to clinical populations, leading to enhanced understanding of pain and improvement of human health.

**Disclosures: C.A. Salcido:** None. **M.K. Geltmeier:** None. **P.N. Fuchs:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.12/Z9

**Topic:** D.03. Somatosensation: Pain

**Support:** MOST 103-2320-B-010-041-MY3

MOST 105-2321-B-010-012

**Title:** Perturbation of central amygdala neuron excitability reduces pain- & anxiety-like behaviors

**Authors: *Y.-L. LIN**, C.-C. LIEN
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**Abstract: Abstract**
Chronic pain disorder is associated with anxiety- and depression-like behavior. Although the amygdala is thought as a key node of the neural circuits mediating emotions, it also serves a major receiver of purely nociceptive signals. However, the circuit mechanisms by which the amygdala contributes to the pain-related anxiety has remained unclear. Here, we investigated circuit mechanisms underlying comorbid symptoms in chronic pain mouse models, including acid-induced muscle pain and spinal nerve ligation-induced neuropathic pain. We first found that the phosphorylated ERK (pERK) level increased in the lateral subdivision of central amygdala (CeL) after chronic pain development. To address the role of the CeL in chronic pain, we attempted to manipulate CeL neurons using chemo- and opto-genetic approaches. We hypothesized that silencing of somatostatin-positive ($SOM^+$) neurons in the CeL, which may

activate CeL output neurons (i.e., $SOM^-$ neuron) and thereby suppresses the CeM projecting neurons, which reduces mechanical sensitivity and chronic pain-related behavior. In chemogenetic part, selective expression of designer receptors exclusively activated by designer drugs (DREADDs) was achieved by injecting a virus encoding Cre-dependent inhibitory DREADDs (i.e., hM4Di receptor) into a SOM-Cre driver, a mouse line specifically expressing Cre recombinase in a major population of the CeL. In optogenetic part, we expressed inhibitory halorhodopsin (eNpHR) in $SOM^+$ cells in the CeL. Consistent with this hypothesis, we found that both chemo- and opto-genetic silencing of $SOM^+$ neurons in the CeL reduced mechanical sensitivity and comorbid anxiety-like behavior.

**Disclosures: Y. Lin:** None. **C. Lien:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

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**Program#/Poster#:** 485.13/Z10

**Topic:** D.03. Somatosensation: Pain

**Support:** MOST 104-2320-B-039-020-MY2

MOST 103-2320-B-039-008-

DMR-106-004

**Title:** $H_1$-antihistamines promote electroacupuncture analgesia

**Authors: *Y.-H. CHEN**[1,2], I. MACDONALD[2], H.-Y. CHUNG[2]
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**Abstract:** Acupuncture has been used to treat disease for over 2,500 years. Acupuncture has become a popular treatment modality in Western countries. This study investigated the influence of the histamine $H_1$ receptor antagonists, chlorpheniramine and pyrilamine, on the analgesic effects of acupuncture in mice. Nociceptive response was evaluated by the acetic acid-induced abdominal writhe test. Electroacupuncture (EA) at bilateral ST36 reduced the manifestations of acetic acid-induced abdominal writhing, whereas needle insertion without electrostimulation had no such effect. The analgesic effect of EA was reversed by naloxone pretreatment. While administration of chlorpheniramine (0.6 mg/kg; p.o.) or pyrilamine (2.5 mg/kg; i.p.) as monotherapy did not affect acetic acid-induced abdominal writhing, the combination of each agent with EA reduced the manifestations of abdominal writhing by a greater extent compared with EA alone. The effects of chlorpheniramine on acupuncture analgesia were not completely reversed by pretreatment with naloxone. Acetic acid also induced increases of phospho-p38 expression in spinal cord by Western blot analysis. These effects were reversed by EA-ST36 or

low doses of histamine $H_1$ receptor antagonists. Clearly, histamine $H_1$ receptor antagonists at relatively low doses facilitate EA analgesia via non-opioid receptors. These results suggest a useful strategy for increasing the efficacy of EA analgesia in the clinical situation.

**Disclosures: Y. Chen:** None. **I. MacDonald:** None. **H. Chung:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.14/Z11

**Topic:** D.03. Somatosensation: Pain

**Support:** PAPIIT-IA2013716

FESI-DIP-PAPCA-2016-12

**Title:** Mental nerve constriction as a multidimensional model to study trigeminal neuropathic pain in rodents

**Authors: *C. D. MONTES-ANGELES**, C. ACEVEDO-ROQUE, N. GUTIÉRREZ-CASTAÑEDA, C. SOSA-HUERTAS, M. GARCÍA-JACOME, I. PÉREZ-MARTÍNEZ
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**Abstract:** In order to study the pathophysiology and pharmacology of orofacial neuropathic pain in a multidimensional way, we use surgical and behavioral procedures to study trigeminal neuropathic pain in rats. The mental nerve is subjected to a chronic constriction injury (mNC) by loosely ligating the nerve. In the sensorial
evaluation of chronic pain in this model, rats exhibit changes in spontaneous behavior and in response to von Frey stimulation that are indicative of persistent pain and mechanical allodynia; in the same way the rats show thermic hyperalgesia. The spontaneous activity functions as pain indicator; 15 days post
mNC, rats decrease facial grooming activity, and both allodynia and hyperalgesia decrease as well. After this time, we evaluate the hedonic and cognitive dimension in this model. Using a progressive ratio schedule, we determine an important decrease in motivation for sucrose solution and cognitive alterations in learning,
persistence, familiar memory and adaptation process no regarding with pain, but regarding with chronic changes in circuits at central nervous system induced by orofacial pain.
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**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.15/Z12

**Topic:** D.03. Somatosensation: Pain

**Title:** Aggravation of inflammatory pain after sound stress exposure

**Authors: *C. HUNG**
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**Abstract:** Stress is a well-known trigger of several pain syndromes, including fibromyalgia and painful inflammatory diseases. To simulate these clinical conditions, sound stress models use unavoided sound stimulus to aggravate algesics-mediating pain responses (e.g. cytokines and prostaglandins). So far, comprehensive behavioral studies have not been investigated, and information of co-morbid symptoms and therapeutic responses remain lack. In addition, mechanisms of peripheral nociceptive activation have been seldom studied. Our study indicated not only mechanical but also thermal hyperalgesia developed in the stressed mice. Sound stimulus alone didn't change nociceptive threshold but enhance pain response. Our study also suggested stressed mice developed behaviors of anxiety, fatigue, and visceral hyperalgesia evidently. Regarding therapeutic responses, sound stress mice had similar pharmacotherapeutic responsiveness to clinical pharmacological agents. With addition of algesic substances, nociceptive activation was absent in peripheral sensory neurons in immunostaining study. No evidence of nerve injury was observed. These results helped to elucidate the validity of the current model, and also helped to better understand the potential peripheral mechanism.

**Disclosures: C. Hung:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** D.03. Somatosensation: Pain

**Support:** Veterans Affairs Senior Research Career Scientist Award

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Louisiana Board of Regents ITRS-015B

Louisiana Board of Regents Fellowship

**Title:** Evaluation of ZH853, a novel endomorphin analog, versus morphine in acute and long term dosing for chronic pain

**Authors: *A. K. FEEHAN**[1], X. ZHANG[3], A. T. AMGOTT-KWAN[2], J. E. ZADINA[4,3,5]
[1]Neurosci. Program, [2]Neurosci., Tulane Univ., New Orleans, LA; [3]Med., Tulane Univ. Sch. of Med., New Orleans, LA; [4]SE Louisiana Veterans HCS, New Orleans, LA; [5]Pharmacol., Tulane Univ. Med. Sch., New Orleans, LA

**Abstract:** Over 100 million Americans suffer from chronic pain and many of them are inadequately treated. Although opioids work well against many types of chronic pain, significant side effects deter patients and physicians from using them for these conditions. We have developed a mu-opioid receptor selective endomorphin (EM) analog (ZH853) that does not cause the side effects of currently used opioids including: abuse liability, respiratory depression, motor impairment, tolerance, and glial activation (1). In the current study, we evaluated acute and chronic dosing of ZH853 and morphine in chronic pain states. Both intravenous and intrathecal administration of ZH853 produced a long lasting reversal of hypersensitivity compared to morphine acutely, providing up to two additional hours of pain relief. We are also evaluating the use of chronic, moderate doses of ZH853 and whether it prolongs chronic pain as has been shown with morphine (2). We used classical pain tests (e.g. von Frey) to determine pain sensitivity, while assessing functional recovery with a multitude of gait parameters from the CatWalk XT system. Using these tests, we will determine whether functional and pain recovery correlate, and whether ZH853 or morphine alters the trajectory of recovery.
(1) Zadina, JE *et al.* (2016). *Neuropharmacology* **(105)**: 215-227.
(2) Grace, PM *et al.* (2016). *Proc Natl Acad Sci USA* **(113)**: E3441-3450.

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**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

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**Program#/Poster#:** 485.17/Z14

**Topic:** D.03. Somatosensation: Pain

**Support:** R44 NS086343

43DE026094

R44AG043203

**Title:** A painful neuroma model in rats is objectively assessed using the automated neurobehavioral monitoring system - smartcage™

**Authors: *X. S. XIE**, C. PASCUAL, B. ZOU, W. S. CAO, K. XIAO, O. V. HORST
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**Abstract:** Traumatic nerve injury or postoperation-induced neuroma formation occur in approximately 30% of cases and are one of the main causes of neuropathic pain. Painful neuroma is particularly difficult to treat since it usually responds poorly to all existing therapies including local injection of lidocaine and systemic medication of gabapentin or other analgesics such as opioids. To develop a more effective, non-opioid analgesic, translational animal models and face-validity tests must be established. The tibial neuroma transposition (TNT) in rats is a model of painful neuroma that has been reported.
After establishing the TNT model in rats, we used AfaSci's noninvasive rodent neurobehavior monitoring system SmartCage™ to assess neuroma pain effects on rodent homecage activity. In parallel, we conducted conventional mechanical pain measurements with von Frey monofilaments and used current therapies to validate the objective and automated assessment. After measuring baseline of the pain threshold and homecage activity of individual rats, the posterior tibial nerve was exposed and the calcaneal branch was dissected free from the main trunk of the tibial nerve under anesthesia. The surgical rats were then returned to their homecages. A neuroma gradually formed in around 70% of rats operated which was confirmed histopathologically. Persistent pain associated with neuroma developed over a 2-3 week period indicated by an increase in mechanical hypersensitivity assessed using a peri-neuromal mechanical allodynia test on the skin overlying the neuroma, and in the ipsilateral hindpaw in respect with the contralateral side of the same subject, or compared to sham animals. The SmartCage recorded for 1 - 3 days and showed decreases in active time, travel distance, speed, and especially rearing in neuroma rats compared to sham control.
Intradermal injections of 1.5% lidocaine (50µl x 2) around the neuroma or oral administration of gabapentin (50-100mg/kg) restored the four behavioral parameters to the sham level and significantly decreased allodynia compared to control. The TNT model and the combined assessment of mechanical pain thresholds and homecage activity are now being employed in-house to evaluate new compounds that modulate key targets that play critical roles in the pain signaling pathway.

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**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.18/Z15

**Topic:** D.03. Somatosensation: Pain

**Support:** NIH T32 Training Grant

**Title:** Classifying mouse pain faces using a machine learning algorithm

**Authors: *A. H. TUTTLE**[1], M. MOLINARO[3], M. J. ZYLKA[2]
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**Abstract:** By adapting the human action coding system, researchers have recently discovered that facial expressions are conserved across a variety of mammalian species. The Mouse Grimace Scale (MGS) is one such adaptation that allows researchers to quantify mouse pain faces and assess spontaneous pain (Langford et al., 2010). Despite advances to automate image collection, the MGS still relies on trained laboratory personnel to asses the presence of pain faces, preventing the widespread use of this behavioral assessment. Here we adapt and train a convolutional neural network (Google TensorFlow) on over 2000 mouse face images to quickly and accurately assess the presence of grimacing in novel images. Coupled with the previously published Rodent Face Finder (c) we outline a viable pipeline that will allow untrained personnel to take recorded footage of mice and quickly determine the presence of pain from a large number of samples. We also show a degree of granularity in mouse grimacing that was not possible with human coding.

**Disclosures: A.H. Tuttle:** None. **M. Molinaro:** None. **M.J. Zylka:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.19/Z16

**Topic:** D.03. Somatosensation: Pain

**Support:** NIH Grant NS6768

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NIH Grant DE22743

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NIH Grant MH104326

**Title:** Pain in Autism: SHANK3 deficiency in sensory neurons impairs mGluR5-induced signaling via peripheral and presynaptic modulation

**Authors: *L. ZHANG**[1], Q. HAN[2], H. LUO[2], Y. KIM[2], X. WANG[2], Y.-H. JIANG[2], R.-R. JI[2]
[1]Anesthesiology, Duke Univ., Durham, NC; [2]Duke Univ., Durham, NC

**Abstract:** Self-injurious behaviors are considered a devastating trait in autism spectrum disorder (ASD). Although pain-related sensory abnormalities may be a pivotal determinant in this process, the mechanisms have yet to be understood. SHANK3, a postsynaptic scaffold protein, is strongly implicated in the pathogenesis of ASD-related phenotypes. SHANK3 deletion results in dysfunction of metabotropic glutamate receptor 5 (mGluR5), suggesting a link between SHANK3 and mGluR5 in ASD. Recently, we found that SHANK3 is expressed by DRG primary sensory neurons and regulates TRPV1 function and heat hyperalgesia (Han et al., Neuron, 2016, PMID:27916453). Given an important role of mGluR5 in pathological pain, we tested the hypothesis that mGluR5 is also a target of SHANK3 in primary sensory neurons, using *Shank3* conditional knock-out (CKO) mice with specific loss of SHANK3 in Nav1.8-expressing sensory neurons. We tested mGluR5-mediated spontaneous pain and mechanical pain following both central (intrathecal) and peripheral (intraplantar) administration of mGluR5 agonist DHPG. CKO mice exhibited a marked reduction in DHPG-induced spontaneous pain after intrathecal injection. CKO mice also showed a reduction in DHPG-induced mechanical allodynia after intraplantar injection. Furthermore, mGluR5 expression in DRG and spinal dorsal horn tissue is downregulated in CKO mice. We are currently investigating the mGluR5-mediated synaptic transmission in the spinal cord of CKO mice. Our findings suggest that peripheral and presynaptic regulation of mGluR5 expression by SHANK3 may be an important mechanism of SHANK3-related pain deficits in ASD.

**Disclosures: L. Zhang:** None. **Q. Han:** None. **H. Luo:** None. **Y. Kim:** None. **X. Wang:** None. **Y. Jiang:** None. **R. Ji:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.20/Z17

**Topic:** D.03. Somatosensation: Pain

**Support:** JUST 20150343

**Title:** Antinociceptive effects of NSAIDs on acid-stimulated stretching and acid-depressed feeding in rats

**Authors: *A. ALTARIFI**[1], B. YOUNIS[2], M. ALSALEM[3], K. NUSEIR[2]
[1]Jordan Univ. of Sci. and Technol., Zarqa, Jordan; [2]Jordan Univ. of Sci. and Technol., Irbid, Jordan; [3]The Univ. of Jordan, Amman, Jordan

**Abstract:** Pain is a major problem that burden the health and economy of societies worldwide. The main pharmacological treatments of pain include nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Because of their side effects, new analgesics are needed to improve pain management clinically. The main aim of our study was to establish new animal models to enable investigators to assess antinociceptive effects of candidate analgesics in comparison to currently used analgesics. Thus, we studied the antinociceptive effects of different NSAIDs in inflammatory pain conditions in rats. Noxious stimuli can produce pain-stimulated behaviors and pain-depressed behaviors. Effective analgesics are determined by blocking both behaviors. Here, we used intraperitoneal lactic acid as noxious stimulus to produce acid-stimulated stretching and acid-depressed feeding. Next, we assessed the efficacy of ibuprofen, diclofenac, naproxen, and acetaminophen on acid-stimulated stretching and acid-depressed feeding behaviors in adult male Fischer rats. We hypothesized that NSAIDs will block acid-stimulated stretching and acid-depressed feeding. In stretching studies, lactic acid produced dose-dependent increase in stretching, that was significant after 1.8%, which was used in subsequent studies. In feeding studies, rats were allowed to eat regular chow for 1 hour after different durations of food restriction. 24 hours of food restriction was selected for subsequent feeding studies. Afterward, lactic acid produced dose-dependent decrease in food consumption, that was significant after 3.2% lactic acid which was used in subsequent studies. ibuprofen reduced lactic acid-stimulated stretching and acid-depressed feeding behaviors after 10 and 32 mg/kg, respectively. 10 mg/kg Diclofenac and 100 mg/kg acetamoniphen reduced both acid-stimulated stretching and acid-depressed feeding behaviors. Also, 3.2 mg/kg of naproxen reduced lactic acid-stimulated stretching behavior only. These data showed that feeding behavior provides good preclinical animal model to assess nociception pain and antinociceptive effects of drugs, especially if combined with pain-stimulated behaviors. Finally, there was comparable efficacy between tested NSAIDs in both acid-stimulated stretching and acid-depressed feeding.

**Disclosures:** **A. Altarifi:** None. **B. Younis:** None. **M. Alsalem:** None. **K. Nuseir:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.21/Z18

**Topic:** D.03. Somatosensation: Pain

**Title:** Differential patterns of glial expression in the hippocampus of rats with behavioural changes following nerve injury

**Authors: *N. T. FIORE**, P. J. AUSTIN
Anat. and Histology, Univ. of Sydney, Sydney, Australia

**Abstract: Aims**: Chronic constriction injury (CCI) evokes sensory 'pain' in all rats, and evokes affective-motivational disturbances in a sub-population. We examined whether foraging behaviour and spatial memory on the radial maze task as well as glial expression in the hippocampus were altered after CCI. **Methods**: Outbred male Sprague-Dawley rats underwent daily radial maze testing for 14 days after CCI (n=32) or sham injury (n=10). Rats were habituated to the radial maze prior to testing. During each test 4 arms were baited with sucrose pellets and rats were given 5 minutes to complete the task. Foraging behaviour was assessed with the 'time in the central atrium per entry' (an index of risk-assessment) recorded. Working memory errors (an index of spatial memory) were also recorded. Rats also underwent von Frey and rota-rod testing. Immunofluorescent labelling of GFAP (n=6 sham and n=18 CCI) and IBA-1 (n=4 sham and n=12 CCI), with a detailed anterior/posterior-dorsal/ventral analysis conducted to quantify % immunoreactivity (-IR) of astrocytes and microglia respectively within sub-fields of the hippocampus (cornu ammonis, dentate gyrus and subiculum). **Results**: CCI reduced withdrawal thresholds and motor activity in all rats and no differences in spatial memory were observed, whilst foraging behaviour was altered in some but not all rats. One group (n=12), termed '*No effect*', had no behavioural changes compared to sham injured rats. Another group (n=8), termed '*Acute effect'*, had a temporary 3-standard deviation (SD) increase in their risk-assessment on the initial 7 days post-injury. In a third group (n=12), termed '*Lasting effect*', rats displayed a sustained 3SD increase in their risk-assessment for the entire post-injury period. There was no change in astrocyte or microglia-IR between CCI and sham rats. *Lasting effect* rats displayed reduced astrocyte-IR in the contralateral posterior dentate gyrus ($p<0.05$ n=6 from each group) and reduced microglia-IR in the contralateral ventral cornu ammonis ($p<0.05$ n=4 from each group) relative to *No effect* rats. **Conclusions**: These data highlight that nerve injury drives three differing phenotypes of foraging behaviour on the radial maze task. Considering the degree of sensory 'pain' does not predict development of behavioural changes clinically, the decoupling of allodynia from the changes in foraging behaviour triggered by nerve injury are indicative of the clinical relevance of this model. Further, differential patterns of glial expression

in the contralateral ventral hippocampus across nerve-injured rats may predispose the *Lasting effect* group to the development of affective-motivational disturbances after CCI.

**Disclosures:** **N.T. Fiore:** None. **P.J. Austin:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.22/Z19

**Topic:** D.03. Somatosensation: Pain

**Support:** Rita Allen Foundation and American Pain Society

**Title:** Pain tolerance measured with the Operant Plantar Thermal Assay is altered in inflammatory and neuropathic pain models

**Authors: *A. N. REKER**[1], S. CHEN[2], S. DAVIDSON[1]
[1]Anesthesiol., [2]Univ. of Cincinnati, Cincinnati, OH

**Abstract:** We developed a novel apparatus: the Operant Plantar Thermal Assay (OPTA). The OPTA has dual chambers, each having independently thermally adjustable floors and a reward zone, requiring an animal to engage in decision-making and evaluation of pain tolerance to cross the investigator-set thermal stimulus to obtain a reward. The time and count spent traversing the noxious floor and entering the reward zone are indices of the level of pain an animal is willing to accommodate to receive a reward and thus a gauge of pain tolerance. Results show that baseline reward access was highest when the floor was set to 40°C, and dropped significantly when set below 10°C and above 45°C, indicating that floor temperatures in the noxious range were less tolerated. We further validated the OPTA using models of inflammatory (complete Freund's adjuvant, CFA) and neuropathic (chronic constriction injury, CCI) pain. CFA injected to the mouse hind paw resulted in reduced time in the 45°C zone compared to the 30°C zone, as well as less time in the reward zone. When administered to mice pre-treated with CFA, the nonsteroidal anti-inflammatory Meloxicam resulted in significantly increased time spent in the reward zone suggesting increased pain tolerance. CCI resulted in reduced overall time in the uncomfortable zone, but an increase in time spent in the reward zone. Parallel studies in our lab show that anterior cingulate cortex (ACC) mGluR2$^+$ neurons exhibit hyperexcitability in a model of persistent inflammatory pain and that this is effectively reversed, *in vitro*, via administration of an mGluR2$^+$ agonist. We hypothesized that mGluR2+ ACC neurons are involved in regulating higher order pain processing, such as establishing pain tolerance level, which requires limbic and cognitive processing. Therefore, we examined whether *in vivo* pain-related behaviors are influenced by direct infusion of the mGluR2$^+$ agonist, (2R-4R)-4-aminopyrrolidine-2-4-

dicarboxylate (APDC) to the ACC as well as optogenetic manipulation of *GRM2+* ACC neurons in *GRM2*x*ChR2*-EYFP mice that we generated.

**Disclosures: A.N. Reker:** None. **S. Chen:** None. **S. Davidson:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.23/Z20

**Topic:** D.03. Somatosensation: Pain

**Support:** Mechanisms for Trigeminal Neuralgia/ Facial Pain Research Foundation

NIH R00AR057426

**Title:** Behavioral characteristics of capsaicin mediated cutaneous, myogenic, and arthrogenic orofacial nociception in rats

**Authors: E. L. ROHRS**[1], J. K. NEUBERT[1], K. D. ALLEN[2], *R. M. CAUDLE[3]
[1]Orthodontics, [2]Biomed. Engin., Univ. of Florida, Gainesville, FL; [3]Dept Oral Surg, UFCD, Gainesville, FL

**Abstract: Objective**: To assess changes in orofacial mechanical sensitivity and gnawing in rat models of capsaicin mediated cutaneous, myogenic, and arthrogenic nociception. **Design**: To assess cutaneous sensitization, eleven female CD-Hairless rats were tested with bilateral capsaicin cream application to the cheek or with isoflurane anesthesia alone. After recovery from anesthesia, orofacial mechanical sensitivity and gnawing were assessed using operant testing methods. Following a few weeks of recovery, animals received either 10 µL unilateral masseter injections of capsaicin solution (1%), vehicle, or PBS. Again, after recovery from anesthesia, orofacial mechanical sensitivity and gnawing were assessed. Finally, animals received either 10 µL unilateral TMJ injections of capsaicin solution (1%) or vehicle, with mechanical sensitivity and gnawing assessed after recovery from anesthesia. **Results**: Capsaicin cream to the skin significantly affected gnawing (increased puncture time by 338.5 seconds) and orofacial mechanical sensitivity (decreased tolerated bottle distance by 0.227 inches). Similarly, capsaicin injection to the masseter significantly affected gnawing (increased puncture time by 424.7 seconds) and orofacial mechanical sensitivity (decreased tolerated bottle distance by 0.360 inches). However, intra-articular capsaicin in the TMJ only affected gnawing (increased puncture time by 207.9 seconds), with no changes found in orofacial mechanical sensitivity. **Conclusion**: Capsaicin masseter injections and cutaneous application of capsaicin cream had similar behavioral effects; however, intra-articular injections to the TMJ only affected gnawing. These

data indicate that the behavioral changes in a rodent models of myogenic and cutaneous pain may be markedly different than models of arthrogenic pain originating from the TMJ.

**Disclosures:** **E.L. Rohrs:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Velocity Laboratories. **J.K. Neubert:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Velocity Laboratories. **K.D. Allen:** None. **R.M. Caudle:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Velocity Laboratories.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.24/Z21

**Topic:** D.03. Somatosensation: Pain

**Support:** Al-Ahliyya Amman University

**Title:** Antinociceptive effect of the methanol extract from ajuga chamaepytis

**Authors: *S. M. JAFFAL**[1], M. A. ABBAS[2]
[1]Pharmaceut. Sci., [2]Al-Ahliyya Amman Univ., Amman, Jordan

**Abstract:** *Ajuga chamaepitys* is a small herbaceous perennial plant belonging to Lamiaceae family. It is one of the medicinal plants that grow in the Middle East and has several therapeutic effects in the treatment of rheumatism, sclerosis, jaundice and gout. In this study, we examined the antinociceptive effect of the methanol extract of *Ajuga Chamaepytis* collected from Jordan. The antinociceptive effect of the extract was studied using chemical (acetic acid writhing test and formalin induced nociception test) and thermal (hot plate) pain models in BALB/c mice. Our data showed that the intraperitoneal (i.p) injection of 300 mg/kg of *A. chamaepitys* extract (for 30 min) decreased the number of writhes that were induced in mice by the acetic acid injection (i.p), significantly, compared to negative control group. In addition, the treated animals showed a remarkable decrease in the time of paw licking in the second, but not the first, phase of formalin induced paw licking test suggesting the involvement of the central sensitization as a possible mechanism of action for the methanol extract of *A. chamaepitys*. Furthermore, the treatment with *A. chamaepitys* extract increased *the latency of paw licking and the jumping responses by 3 folds compared to non-treated animals* in hot plate test indicating the analgesic effect of the extract in this thermal test. In summary, our results suggest that the methanol extract of *A. chamaepitys* has pronounced antinociceptive effects and can have promising therapeutic applications in pain. The mechanism of action is being currently investigated in our lab.

**Disclosures:** **S.M. Jaffal:** None. **M.A. Abbas:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.25/Z22

**Topic:** D.03. Somatosensation: Pain

**Support:** PAPIIT-IA2013716

FESI-DIP-PAPCA-2016-12

**Title:** Binge-type ethanol consumption increased by trigeminal injury and periodontal lesion in rats

**Authors: M. MARTÍNEZ-ORDOÑEZ**[1], B. LOPEZ-NIETO[1], R. ACEVEDO-ROQUE[1], M. GARCÍA-JACOME[1], D. L. SOLIS-SUAREZ[2], A. L. GARCÍA-HERNÁNDEZ[2], *I. O. PEREZ-MARTINEZ[1]
[1]Lab. of Neurobio. of Oral Sensations, Cuautitlán Mexico, Mexico; [2]Lab. of osteoinmunology, UNAM, Mexico

**Abstract:** Chronic pain is a condition in which pain no longer functions as a defense mechanism, but as a neuroplastic alteration in the structures that integrate pain and other vital functions, in addition to reducing the quality of life of those who suffer from it. Various investigations have revealed a possible overlap between brain regions involved in pain modulation and susceptibility to developing alcoholism, including structures of the limbic system. On the other hand, periodontal disease is a common, inflammatory, infectious and painless pathology that affects dental support tissues. It has been associated with diabetes mellitus, cardiovascular disease, rheumatoid arthritis, psoriasis, stress, oral cancer, and mental illness. The present study aimed to validate the increase in binge-type ethanol consumption induced by chronic neuropathic pain caused by constriction of the mental nerve and periodontal lesion. Forty five male Wistar rats, with an initial weight of 300 to 400g, were divided into 4 groups: 2 experimental groups; 1 of surgery with mental constriction [CCNM] and 1 group with periodontal lesion [LP], and 2 groups with sham surgery. For alcohol consumption, the drinking-in-the-dark model was used, starting on the postoperative day 48 for the LP group and 52 for the CCNM group. Immediately after the baseline days, a 10% ethanol concentration was used; afterwards, it was increased to 20 and 40% by carrying out the same protocol. The results showed that the constriction of the mental nerve and periodontal disease were factors that considerably increased the binge eating of ethanol without correlating with the degree of spontaneous pain. The present work shows evidence for the first time, that chronic inflammatory and neuropathic orofacial pain may

generate alterations in neuronal circuits of the central nervous system that induce alcoholism.
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**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.26/Z23

**Topic:** D.03. Somatosensation: Pain

**Support:** T32 COSTAR DE14318

R01 GM06075

**Title:** Contribution of anoctamin 1 to burn injury hypersensitivity

**Authors: *A. WALLACE**[1], K. M. HARGREAVES[2]
[1]Endodontics, Univ. of Texas Hlth. Sci. Ctr. At San A, San Antonio, TX; [2]Endodontics, UT Hlth. Sci. Ctr. at San Antonio, San Antonio, TX

**Abstract:** Persistent pain associated with burn injury is a major clinical challenge primarily due to the lack of efficacious analgesics. Although opioids are the gold standard for pain control, their efficacy in burn injury is insufficient and dosage increases are limited by their fatal side effect of respiratory depression. Thus, exploring mechanisms underlying burn injury-related pain is essential for developing more effective treatments with fewer side effects. Previously, we developed a mouse model of burn injury that recapitulates the persistent thermal and mechanical hypersensitivities reported clinically. In this study, we investigated the contribution of ANO1 in our burn model at a time-point corresponding to peak hypersensitivity post-burn. We determined that an intraplantar injection of a selective ANO1 antagonist, dose-dependently attenuated burn injury-evoked thermal and mechanical hypersensitivity. Preliminary analysis of mRNA transcript levels indicates that ANO1 expression is reduced in skin biopsies from the ipsilateral hindpaw 4 days following induction of burn injury. ANO1 transcript levels were unchanged in lumbar DRG or spinal cord. To provide a neurophysiological correlate to burn injury-induced hypersensitivity observed behaviorally, we investigated spontaneous and stimulus-evoked response properties of sensory nerve fibers innervating burn-injured glabrous skin at peak hypersensitivity. Pain-transducing sensory nerve fibers were activated at lower mechanical forces and displayed increased spontaneous firing in burn-injured glabrous skin relative to sham controls. Furthermore, in congruence with clinical reports, we detected a decrease in C-fiber conduction

velocity from burn-injured skin preparations. The complementary behavioral and electrophysiological approaches provide a means to correlate changes in the transmission of nociceptive signals with the existence of ongoing burn injury-associated pain. Ongoing experiments will further characterize the stimulus-evoked and spontaneous discharge phenotype of sensory neurons at their peripheral terminals and how ANO1 may contribute to burn injury-evoked alterations. Pharmacological modulation of this channel may serve as an effective treatment strategy for ongoing debilitating burn pain in patients.

**Disclosures:** **A. Wallace:** None. **K.M. Hargreaves:** None.

**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.27/Z24

**Topic:** D.03. Somatosensation: Pain

**Support:** MOST104-2314-B-038-034

MOST106-2321-B-001-044

**Title:** Spinal nerve injury distal to dorsal root ganglion causes more persistent pain and more hypoxia than proximal to dorsal root ganglion

**Authors:** ***J.-H. LIN**[1,2], Y.-W. YU[3], C.-C. CHEN[5,6], Y.-H. CHIANG[4,2]
[1]Taipei Med. Univ. Hosp., Taipei, Taiwan; [2]Grad. Inst. of Neural Regenerative Med., Col. of Sci. and Med. Technology, Taipei Med. Univ., Taipei, Taiwan; [3]Grad. Inst. of Neural Regenerative Med., [4]Taipei Med. Univ., Taipei, Taiwan; [5]Academia Sinica, Taipei, Taiwan; [6]Taiwan Mouse Clinic-National Comprehensive Phenotyping and Drug Testing Ctr., Academia Sinica, Taiwan

**Abstract:** In lumbar radiculopathy rat models of constriction in proximity to the dorsal root ganglion (DRG), the animals response differs dramatically dependent on whether the constriction sites distal or proximal to DRG. Although the evidences showed constriction distal to DRG caused more severe radiculopathy than constriction proximal to DRG, the mechanism is largely unknown. The purpose of this study was to compare the severity of radiculopathy following constriction proximal or distal to the DRG by using pain behaviors, the extent of hypoxia, and the ratios of DRG neuron subpopulation. The three pain behaviors tests, 50% paw withdraw threshold, incapacitence test, and acetone test, demonstrated that animals with distal spinal nerve injury had more persistent pain behaviors than those with proximal spinal nerve injury. The optical density of hypoxia-probe 1 as well as the ratios of ATF3-positive DRG neurons were significant higher in distal spinal injury group than those in proximal spinal injury group. The ratio of CGRP+ DRG neurons after distal spinal nerve injury was higher than those after

proximal spinal nerve injury, but the difference did not reach the statistical significance. The ratios of IB4+ or N52+ DRG neuron were not different among three groups. This study demonstrated animals with distal spinal nerve injury presented more persistent pain behaviors and the mechanism may be the more hypoxia and more nerve injury in the DRGs after distal spinal nerve injury.

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**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.28/Z25

**Topic:** D.03. Somatosensation: Pain

**Title:** Pronociceptive effect of calcium-activated chloride channel Bestrophin-1

**Authors: *G. GARCÍA**, R. NORIEGA-NAVARRO, P. A. MUÑOZ-CASTILLO, J. MURBARTIÁN
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**Abstract:** The calcium-activated chloride channels (CaCC) are transmembrane proteins activated by intracellular $Ca^{2+}$ concentration. CaCC are involved in several physiological processes including transepithelial secretion, neuronal excitation, neuronal regeneration and sensory transduction. Bestrophin-1 (Best-1) belongs to the family of CaCC and it was the first channel to settle within this family. Although Best-1 is expressed in dorsal root ganglion (DRG) neurons and participate in regeneration processing, the function in DRGs of this channel is not complete known. It has been reported that CaCC currents increase after sciatic nerve axotomy. Previously, we determine that Best-1 protein expression strongly increase after L5 spinal nerve axotomy than L5/L6 spinal nerve ligation. Thus, Best-1 may contribute to maintain nociceptive behaviors in neuropathic pain induced by lesion of spinal nerves.
The aim of this study was to determine the nociceptive effect of up-regulation of Best-1 expression in naïve rats. *E. coli* bacteria were transformed with a plasmid that contain a Best-1 DNA sequence (pCMV6-Best1). The plasmid was isolated and identified by PCR and restriction enzyme digestion. After that, we realized intrathecal injection (i.t., into the subarachnoid space, between L4 and L5 disc) of pCMV6-Best1 10µg during 3 days and determined mechanical tactile allodynia in naïve rats. Besides, we determined protein expression of Best-1, neuronal injury marker ATF-3, apoptosis marker caspase-3 and neuronal regeneration marker GAP-43, in L4 and L5 DRG neurons by western blotting. I.t. injection of Best-1 plasmid increased the protein expression of this channel in L4 and L5 DRGs. Moreover, up-regulation of Best-1

developed nociceptive behaviors. Our results suggest that Best-1 channels have a pronociceptive role.

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**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 485.29/Z26

**Topic:** D.03. Somatosensation: Pain

**Support:** European Research Council

Adelson Medical Research Foundation

**Title:** An importin alpha knockout mouse with attenuated pain responses

**Authors: *L. MARVALDI**[1], N. PANAYOTIS[1], S. Y. DAGAN[1], I. RISHAL[1], K. COHEN-KASHI[2], F. ROTHER[5], N. OKLADNIKOV[1], V. BRUMFELD[3], Y. ADDADI[4], E. HARTMANN[5,6], M. BADER[5], M. FAINZILBER[1]
[1]Dept. Biomolecular Sci., [2]Dept. Neurobio., [3]Dept. Chem. Res. Support, [4]Dept. Biol. Services, Weizmann Inst. of Sci., Rehovot, Israel; [5]Max Delbrück Ctr. for Mol. Med., Berlin-Buch, Germany; [6]Inst. for Biol., Univ. of Lübeck, Lübeck, Germany

**Abstract:** Nuclear import factors from the importins family are involved in dendritic, axonal and nuclear transport mechanisms in neurons, but their physiological importance is still not clearly understood. We have found sensory deficits in an importin alpha KO mice, most prominently a significantly reduced responsiveness to noxious heat, together with changes in axonal growth and morphology in the sciatic nerve. In order to understand the underlying molecular mechanisms we performed RNA seq analyses on wild type versus embryo dorsal root ganglia (DRG) followed by bioinformatics analyses. The results show changes in c-FOS dependent transcription in KO DRG, with a corresponding mislocalization of c-FOS out of the nucleus in KO neurons. Since c-FOS has been implicated in pain signaling via unknown mechanisms, these findings raise the possibility that the reduced heat sensitivity in an importin alpha KO mice are actually due to a c-FOS nuclear import deficit in these animals.

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**Poster**

**485. Pain Models: Physiology and Behavior II**

**Location:** Halls A-C

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**Topic:** D.03. Somatosensation: Pain

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**Title:** Distinct functions of alternatively spliced intracellular carboxyl termini of mu opioid receptors on morphine action

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**Abstract:** Extensive alternative splicing of the mu opioid receptor (OPRM1) gene creates an array of splice variants that are conserved from rodent to human. Of these splice variants, the carboxyl (C-) terminal 7 transmembrane (TM) variants share an identical receptor structure, but have a different intracellular C-terminal tail. Although several C-terminal 7-TM variants have been characterized in vitro for agonist-induced G protein coupling, phosphorylation, internalization and post-endocytic sorting, their in vivo functions remain largely unknown. The present study generates three mutant mouse models truncating either all C-terminal tails or only C-terminal tails encoded by exon 4 or exon 7 in two different inbred strains, C57BL/6J (B6) and 129/SvEv. Characterizing these mice reveals divergent roles of individual C-terminal tails in various morphine actions, such as tolerance, physical dependence, locomotor activity and reward, highlighting the importance of individual intracellular C-terminal tails in mediating

complex morphine actions. For example, truncating exon 7 (E7)-associated C-terminal tails in B6 mice (mE7M-B6) attenuated morphine tolerance and reward with no change in morphine dependence, whereas truncating exon 4 (E4)-associated C-terminal tails in B6 mice (mE4M-B6) facilitated morphine tolerance and reduced morphine dependence without affecting morphine reward. Truncating E7-associated C-terminal tails in B6 mice resulted in loss of morphine-induced receptor desensitization in the hypothalamus and brainstem, consistent with exon 7 involvement in morphine tolerance. Down-regulating E7-associated C-terminal variants with an antisense vivo-morpholino oligo mimicked the attenuation of morphine tolerance seen in mE7M-B6 mice, providing potential clinical utility for altering mu opioid action through modulating OPRM1 alternative splicing. Furthermore, the similarity in several morphine-induced behaviors and receptor desensitization between mE7M-B6 homozygous and β-arrestin 2 KO mice suggests a physical and functional association of exon 7-associated C-terminal tails with β-arrestin 2, a hypothesis further supported by our in vitro data showing that several mu agonists displayed greater β-arrestin bias against exon 7-associated variants than against the exon 4-associated mMOR-1. Together, the differential effects of C-terminal truncation illustrate the pharmacological importance of OPRM1 alternative splicing.

**Disclosures:** **J. Xu:** None. **Z. Lu:** None. **A. Narayan:** None. **V.P. Le Rouzic:** None. **M. Xu:** None. **A. Hunkele:** None. **T.G. Brown:** None. **W.F. Hoefer:** None. **G.C. Rossi:** None. **R.C. Rice:** None. **A. Martinez-Rivera:** None. **A.M. Rajadhyaksha:** None. **L. Cartegno:** None. **D.L. Bassoni:** None. **G.W. Pasternak:** None. **Y. Pan:** None.

**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

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**Topic:** D.03. Somatosensation: Pain

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**Title:** Dysgranular area in somatosensory cortex of mice represents nociceptive information

**Authors: *H. OSAKI**, Y. UETA, M. MIYATA
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**Abstract:** It has been extensively studied that cortical representation of tactile information in the granular area of the primary somatosensory cortex (S1). However, cortical representation of nociceptive information is still poorly understood. In this study, to identify the area that receives nociceptive information in S1, we mapped the activated S1 region in neuropathic pain model mice by intrinsic signal optical imaging. To induce neuropathic pain, the infra-orbital nerve that transfers whisker sensory information was ligated. After ligation, we detected the signal in the dysgranular area (Dys) evoked by mechanical whisker stimulation, while the signal in the granular S1 largely reduced. Dys was also activated by a 50°C thermal stimulation. To confirm noxious stimulation activates Dys, we injected capsaicin into the whisker pad and counted the number of neurons expressing c-Fos, a marker of neural activity. Capsaicin injection significantly increased the number of c-Fos positive neurons in Dys, compared to vehicle injection into the whisker pad. These data suggested that Dys represents nociceptive information. It is already known that nociceptive information is processed in the posterior nucleus (Po) in the thalamus and sent to layer 5a in the granular S1. Therefore we anatomically investigated the thalamic input into Dys using anterograde and retrograde labelling. The thalamocortical neurons retrogradely labeled from Dys were found locally in Po, and axonal projections anterogradely labeled from Po were found in layer 4 of Dys. From these observations, we conclude that Dys is a part of the paralemniscal pathway that processes nociceptive information. Because cytoarchitectonic features in mouse Dys are similar to those in human area 3a, which receives nociceptive and proprioceptive information from somatosensory thalamus, our results may be of help to understand the cortical representation of the neuropathic pain in human.

**Disclosures: H. Osaki:** None. **Y. Ueta:** None. **M. Miyata:** None.

**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

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**Topic:** D.03. Somatosensation: Pain

**Support:** NIH Grant K01AT005935

Australian Spinal Research Foundation LG2010-11

**Title:** Alteration of thalamic submedius activity following lumbar spinal thrust

**Authors: *W. R. REED**[1], J. T. CRANSTON[2], S. M. ONIFER[2], J. W. LITTLE[3], R. S. SOZIO[2]
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**Abstract:** Thalamic submedius (Sm) neurons typically have large (bilateral) receptive fields and respond predominately to noxious convergent sensory input from spatially separated cutaneous, muscle, joint, and visceral tissues which suggests a non-discriminatory role in nociception. These characteristics make Sm nociceptive-specific neurons good candidates for investigating supraspinal changes related to manual therapy interventions. The purpose of this study was to determine if lumbar (L5) vertebra high velocity low amplitude thrusts alter spontaneous and/or noxious evoked Sm activity. Extracellular recordings were obtained from 94 Sm neurons in 54 urethane-anesthetized adult male Wistar rats. Spontaneous activity was recorded 5min before and after an L5 control (no thrust) and thrust (85% rat body weight; 100ms) procedure. In a subset of responsive nociceptive-specific neurons, mean changes in noxious evoked response (10s pinch with clip; 795g) at 3 sites (tail, contra- and ipsilateral hindpaw) were determined following an L5 thrust. Mean changes in Sm spontaneous activity (60s bins) and evoked response were compared using repeated measures ANOVA and paired t-tests, respectively. Compared to control, spontaneous Sm activity decreased 180-240s following lumbar thrust ($p<0.005$†). lnhibitory evoked responses were attenuated in the contralateral hindpaw following an L5 thrust compared to control ($p<0.05$*). A delayed, but prolonged suppression of spontaneous Sm activity along with changes in noxious evoked responses in the contralateral hindpaw following lumbar vertebra thrust suggest that thalamic submedius neurons may play a role in central pain modulation related to manual therapy intervention.

Change in Spontaneous Activity (imps)

| | **Control** | | **L5 Thrust** | |
|---|---|---|---|---|
| *Seconds* | *Mean* | *SEM* | *Mean* | *SEM* |
| 60 | 4.75 | 3.65 | -0.93 | 4.31 |
| 120 | 6.36 | 4.42 | -0.88 | 7.72 |
| 180 | 3.35 | 5.56 | 6.64 | 6.16 |
| 240 | 11.63 | 7.39 | -18.39† | 7.13 |
| 300 | 0.98 | 9.03 | -5.43 | 9.22 |

p<0.005†

Change in Noxious Evoked Activity (imps)

| | **Tail** | | **Contra-HP** | | **Ipsi-HP** | |
|---|---|---|---|---|---|---|
| | (n=35) | | (n=43) | | (n=39) | |
| | *Mean* | *SEM* | *Mean* | *SEM* | *Mean* | *SEM* |
| Control | 0.60 | 6.38 | -9.60* | 2.68 | -4.54 | 4.58 |
| L5 Thrusts | -8.51 | 4.82 | -0.84 | 3.49 | 1.26 | 5.91 |
| p<0.05* | | | | | | |

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**Poster**

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**Topic:** D.03. Somatosensation: Pain

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Rita Allen Foundation

NSF Graduate Research Fellowship

**Title:** Excitatory input from the Anterior Cingulate Cortex to the dorsal Periaqueductal Gray facilitates the affective dimension of pain

**Authors: *J. DICKINSON**, G. F. CORDER, A. FRANCOIS, G. SCHERRER
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**Abstract:** Pain is a conscious perceptual experience characterized in large part by its aversive qualities and consequent motivation for relief. Several decades of research have identified the Anterior Cingulate Cortex (ACC), a non-sensory cortical structure, as a critical region for the emotional dimension of pain. In both humans and rodents, acute and chronic pain excites the ACC while lesions and reduced ACC excitability decrease reports of pain being unpleasant. However, the ACC receives diverse inputs from a multitude of brain regions, and responds to a variety of stimuli and circumstances. It thus remains unclear what circuit mechanisms in the

ACC contribute to shaping pain experience. Recent work showed that in prelimbic cortex, a neighboring structure with similarities to the ACC, segregated populations of neurons respond to positively and negatively valenced stimuli. Other studies indicated that the dorsal Periaqueductal Gray (dPAG) is a critical structure for the expression of defensive behaviors and the acquisition of learned responses to aversive stimuli. The ACC projects to the dPAG, but the contribution of this pathway to pain experience has not been resolved. Here, we tested the hypothesis that excitatory input from the ACC to the dPAG during pain facilitates the affective-motivational dimension of pain. First, whole-cell patch-clamp electrophysiology confirmed excitatory transmission between ACC terminals and dPAG Vglut2+, but not Vgat+ neurons. Next, we genetically targeted the ACC neurons projecting to the dPAG with viral vectors to express the hM4Di inhibitory DREADD, and exposed the animals to an assortment of pain tests. We found that inhibition of the ACC-dPAG pathway reduced place avoidance to a noxious heat stimulus as measured by overall increased time spent exploring the noxious zone, increased frequency of zone entries, and increased duration of zone visits. When the noxious stimulus was inescapable, ACC-dPAG inhibition decreased attending-motivational behaviors (such as licking, grabbing, and prolonged lifting), with minimal changes in sensory-reflexive behaviors. In response to mechanical stimuli, ACC-dPAG inhibition reduced attending-motivational nocifensive behaviors and locomotive escape responses. In a neutral environment, inhibition did not change gross motor behaviors, suggesting our pain test results are not merely a reflection of altered motor capacity. Collectively, these results establish the necessity of the ACC-dPAG pathway for the expression of the aversive quality of pain.

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

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**Topic:** D.03. Somatosensation: Pain

**Support:** Rita Allen Foundation and American Pain Society

**Title:** Group II mGluR+ neurons in anterior cingulate cortex are sensitized in mouse models of pain and are positioned to contribute to pain threshold and tolerance behaviors

**Authors: *S. CHEN**[1], S. DAVIDSON[2]
[2]Anesthesiol., [1]Univ. of Cincinnati, Cincinnati, OH

**Abstract:** Anterior cingulate cortex (ACC) is a limbic region associated with emotional processing of pain. Excitatory responses in ACC are predominantly mediated by glutamate receptors. In this study, we focused exclusively on a group of neurons in mouse ACC expressing

Group II metabotropic glutamate receptors subtype 2 (mGluR2), canonically coupled to a Gi/o second messenger pathway. We hypothesized that mGluR2+ neurons in the ACC undergo plastic changes in response to pain. Immunohistochemical studies showed that *GRM2+* neurons, identified by tdTomato expression, were pyramidal type neurons localized to layer 2/3 in the ACC and did not co-express somatostatin or parvalbumin suggesting they are unlikely to be inhibitory interneurons. To study the intrinsic membrane properties of *GRM2+* neurons, we performed whole-cell patch clamp electrophysiology on brain slices containing ACC obtained from adult male and female mice. To explore the characteristics of these cells under persistent peripheral inflammation, we injected the hind-paw with Complete Freund's adjuvant (CFA) and examined *GRM2+* neurons in contralateral ACC 24 hours later. After inflammation, *GRM2+* neurons exhibited significantly higher action potential discharge and sensitized membrane physiology compared to the naïve group. This hyperexcitability was reversed by bath applied (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (APDC, 1 μm), an agonist for mGluR2. Similar results were obtained after the chronic constriction injury neuropathic pain model. In order to determine how ACC affects pain perception, hM4Di-mCherry virus was injected bilaterally into ACC in wildtype mice. Mice subsequently injected with clozapine-n-oxide (CNO, 1mg/kg, i.p.) to activate Gi DREADD showed significantly prolonged paw withdraw latency in a heat plantar test and increased pain tolerance in the Operant Plantar Thermal Assay, compared to a vehicle injected group. Following behavior testing, in vitro slice electrophysiology study was performed to verify injection sites and Gi DREADD activation. hM4Di-mCherry neurons in ACC exhibited decreased membrane potential as well as firing rates after bath application of CNO (5μm). With the goal of specifically modulating mGluR2+ neural activity acutely in the ACC in vivo, we generated GRM2xChR2-EYFP mice and examined light-induced activation of these neurons using whole-cell patch clamp in vitro to determine the optimal parameters for light intensity and pulse frequency for modulation of neural activity. Future studies will test *in vivo* modulation of ChR2 expressing mice to specifically activate GRM2+ neurons in ACC during tests of pain tolerance and threshold.

**Disclosures: S. Chen:** None. **S. Davidson:** None.

**Poster**

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**Topic:** D.03. Somatosensation: Pain

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**Title:** Objective evaluation method for the sudden type of pain

**Authors: *A. NAKAE**, T. SOSHI, Y. TSUGITA
Osaka Univ. Grad. Sch. of Frontier Biosc, Suita-Shi, Japan

**Abstract:** [Background & goal of the study] International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience which leads to the concept that pain is subjective. Everyone must agree that doctors have to treat patients' pain if they say that they feel severe pain. However, for example, doctors sometimes encounter problems due to lack of objective evaluation methods of pain. For example, even after the doctor has administered full strength of the medicine for the specific patient for the pain he/she is experiencing, the patients at times still remain satisfied. This is because patients are not always able to tell that the medicine has already taken effect. To evaluate patients' pain correctly, objective evaluation methods should be developed. The goal of the study is to develop the way to evaluate the sudden type of experimental pain objectively using EEG. [Methods] After signing the written informed consent, 20 healthy volunteers attended the study. Five different electrical stimuli (20, 40, 60, 80,100 microA) were applied randomly using Pain Vision (Nipro Co Ltd., Japan). Participants' subjective evaluation of pain was done using Visual Analog Scale (VAS). Moreover, participants were randomly subjected to 20 pairs of the above mentioned stimulus. The relative rating scale of subjective pain for each electrical stimulus was used as subjective evaluation. Rating were based on the subjective declaration of ("-3: The former is very painful" "0: Neither can you say" "+3: the latter is very painful"), the pairing comparison method of Chefe Method) used for scale. [Results] In the electrical stimulation, median correlation coefficient was 0.91. Discrimination rates between maximum stimulation and middle stimulation was 90%, middle stimulation and minimum stimulation also 90%, whereas maximum and minimum stimulation was 100% based on subjective evaluation and fluctuation of amplitude data.
[Discussion] A close relationship between the stimulation intensity of pain and EEG data is clarified. Objective discrimination of pain can be developed using EEG, and in particular, it must be useful for the patients who cannot describe the amount of pain they are experiencing properly.

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 486.06/AA1

**Topic:** D.03. Somatosensation: Pain

**Support:** Deutsche Forschungsgemeinschaft (DFG), SFB1158 Grants

**Title:** Assessing the functional specialization of prefrontal cortical neurons in acute pain versus non-pain-related processes

**Authors: *O. A. RETANA**, M. J. OSWALD, R. KUNER
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**Abstract:** Structures in the brain involved in nociception are also attributed various functions that are unrelated to pain. The medial prefrontal cortex (mPFC), for example, is not only engaged by painful stimuli, but is also active during memory tasks, decision making, and the processing of emotions like fear, among other contexts. In order to examine the structural correlate that brings about these distinct functions within the same brain region, we address the detailed nature of circuits involving the mPFC in pain and pain-unrelated functions. Our project employs methods with single cell resolution to analyze neuronal activity in different contexts. We use adeno-associated viral vectors expressing marker proteins in an activity-dependent manner to visualize neurons stimulated during acute pain and non-painful conditions. Furthermore, we perform electrophysiological recordings to study the properties of neurons with added temporal precision. We also seek to evaluate the functional contribution of these neural populations to live animal behavior in acute pain and associative learning models. Our experiments promise insights into the cortical circuitry underlying distinct cognitive processes on a cellular level. In addition, this understanding of the microscopic representation of acute nociceptive signaling will enable the investigation of the changes that take place during chronic and pathological pain conditions.

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

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

**Support:** MRC grant MR/M006468/1

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**Title:** Behavioural and cortical pain responses in human infants are dissociable by their relationship to physiological stress

**Authors: *L. JONES**[1], M. LAUDIANO-DRAY[1], K. WHITEHEAD[1], L. FABRIZI[1], J. MEEK[4], M. VERRIOTIS[2], M. FITZGERALD[3]
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**Abstract:** Introduction: In adults, noxious stimulation evokes a cortical pain response and subjective pain report that are modulated by the level of physiological stress. The relationship between pain and stress is proposed to be a significant factor in individual variability of pain perception[1]. In newborn infants noxious stimulation evokes well-described pain behaviour, which is commonly used in place of pain report[2] and nociceptive specific cortical activity (nociceptive Event Related Potential, nERP) as measured with EEG[3]. However, the effect of physiological stress levels upon infant cortical and behavioural pain measures is not known. Here, we investigate this by simultaneously measuring salivary cortisol, heart rate variability (HRV), nERP, and pain behaviour in neonates following a heel lance.
Method: 56 healthy neonates (mean GA 38.8 weeks; mean PNA 3.6 days) were studied during a clinically required heel lance. Ethical approval was given by the UK NRES and UCL/UCLH Joint Research Office.
Cortical activity, time locked to the heel lance, was recorded using EEG[3]. Salivary cortisol and ECG data for HRV calculation were collected before and after the procedure. Pain behaviour was scored using the Premature Infant Pain Profile (PIPP)[2].
Results: The nERP amplitude was positively correlated with the PIPP following a heel lance ($r$=.36, $p$=.033). In addition, higher cortisol concentration and lower HRV, indicative of higher levels of physiological stress, were associated with larger nERP amplitude ($r$=.41, $p$=.029; $r$=-.42, $p$=.027). In contrast, PIPP was unrelated to the level of stress. Interestingly, the direct relationship between the nERP and PIPP was disrupted in babies that had a higher level of physiological stress ($r$=.27, n.s.).
Conclusion: The findings suggest that the cortical nociceptive response provides a more comprehensive measure of the pain experience of infants compared to pain behaviour as it also reflects their level of stress. Moreover, when infants are in a higher state of stress their behaviour in response to a lance is no longer an accurate reflection of the cortical pain processing.
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1. Vachon-Presseau et al. (2013). *J Neurosci*, **33**: 6826-6833.
2. Stevens et al. (1996). Clin J *Pain*, **12**: 13-22.
3. Fabrizi et al. (2011). *Curr Biol*, **21**: 1552-1558.

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

**Location:** Halls A-C

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**Program#/Poster#:** 486.08/AA3

**Topic:** D.03. Somatosensation: Pain

**Support:** FAPESP (Fundação de Amparo à Pesquisa do Estado de Sao Paulo - Brazilian Foundation)

Sirio-Libanes Institute of Research and Teaching

**Title:** Modulation of peripheral inflammatory response and analgesia: Understanding the cortical stimulation effect

**Authors: *D. V. ASSIS**[1], E. T. FONOFF[2], R. L. PAGANO[1]
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**Abstract:** Neuropathic pain (NP) is a complex pain difficult to treat mediated by different mechanisms, including central and peripheral neuroinflammation. Motor cortex stimulation (MCS) is an effective treatment to refractory NP patients, reducing pain in approximately 50% of patients. Our group has shown that MCS reverses the NP in rats by the activation of analgesic descendent pathway, with consequent inhibition of hyperalgesic cytokines release by spinal glial cells, but its mechanisms of action still unclear. In this study, we evaluate the relationship between the MCS-induced analgesia and peripheral cytokine expression in neuropathic animals. Male Wistar rats (45 days) with unilateral chronic constriction injury of the sciatic nerve (CCI) were evaluated in nociceptive tests, submitted to MCS (one session of 15 minutes) and reevaluated in the tests. False-operated (FOP) and CCI unstimulated were used as control. The expression of TNF-α, interleukins-1β, 4, 6, 10 and 17, interferon-γ (IFNγ) and fractalkine (CX3CL1) were analyzed in dorsal root ganglion of the spinal cord (DRG) and in sciatic nerve by multiplex assay. CCI enhanced the expression of IL-1β (57%), IFNγ (23%) and CX3CL1 (29%) in DRG and of CX3CL1 (35%) in sciatic nerve, and conversely inhibited IL-4 (82 %) and IL-10 (37%) in sciatic nerve when compared with FOP. Regardless the therapeutic effect, MCS inhibited TNF-α (20%) and IL-17 (18%) and reversed the increase of IL-1β, IFNγ e CX3CL1 in the DRG while enhanced TNF-α (105%), IL-1β (122%) and IL-6 (411%), inhibited IL-17 (50%) and restored the IL-10 levels in the sciatic nerve. Refractory animals showed a marked increase of IL-1β (28%) and CX3CL1 (26%) in the local of the lesion. The cortical stimulation *per se* modulates the peripheral neuroinflammation, restoring anti-inflammatory IL-10 cytokine level in the local of the lesion and the refractoriness may be correlated with the inflammation status of the injured nerve. Understanding the mechanisms of action of MCS in NP is important to overcome their therapeutic limitations

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

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**Topic:** D.03. Somatosensation: Pain

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**Title:** Multivariate mediation analysis separates functional networks of pain processing

**Authors: *S. GEUTER**[1,2], T. D. WAGER[3], M. A. LINDQUIST[1]
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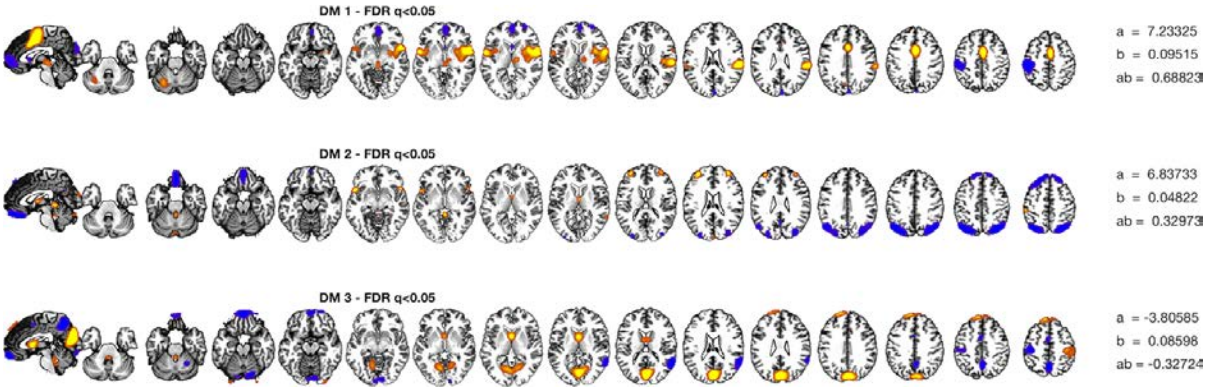
**Abstract:** The brain produces a complex, multi-dimensional experience of pain from nociceptive stimulation, including sensory, emotional, and motivational components. This complexity is reflected by a broad diversity of active brain regions during pain. However, the exact functions and interactions of those brain regions that produce the complex pain experience are not understood.

Here, we aim to identify different functional networks involved in pain perception using a novel multivariate mediation analysis on a large fMRI data set (N=209). The multivariate mediation analysis successively estimates linear combinations of voxels (directions of mediation [DM]) that act as mediators between stimulus intensity and pain report.

Using this novel method, the first DM identified somatosensory areas (including, thalamus, insula, S1, and S2) as well as the PAG, midcingulate cortex (MCC), superior parietal lobe (SPL) and cerebellum as positive mediators of pain (Fig.1). Interestingly, the medial prefrontal cortex and a region encompassing contralateral S1 and M1 contributed negatively, i.e., activity in those regions was negatively related to stimulation intensity and pain reports. These negative mediators were not identified by a standard mediation analysis on the same data. Clustering of the regional responses showed that somatosensory regions and MCC were functionally related to the SPL, a region controlling top-down attention.

The second DM included positive contributions from frontal operculum and lateral prefrontal cortex. Parietal and medial orbitofrontal cortices were negative mediators. The third DM revealed contributions from S1, M1, and parietal regions. Interestingly, contralateral M1 was negatively related to pain, whereas ipsilateral M1 was positively related to pain.

In summary, the novel multivariate mediation analyses identified brain regions contributing to pain beyond the classic somatosensory brain regions and groups them into functional networks that may serve different functional aspects of pain processing.

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**Poster**

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**Program#/Poster#:** 486.10/AA5

**Topic:** D.03. Somatosensation: Pain

**Title:** Modulation of itch in the brainstem monitored by fMRI compared to pain

**Authors: *R. RINGLER**[1], V. VIEROW[2], L. BOETTGER[2], S. KANSY[2], K. DETMAR[3], M. LELL[3], C. FORSTER[2]
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**Abstract:** The experience of pain and itch is a multidimensional phenomenon and can be monitored with fMRI. With a 3 T MRT subcortical areas like thalamus and brain stem as distributing centers of incoming signals as well as areas involved in the modulation can be explored. Itch evokes the desire to scratch to produce relief. But scratch without itch in the background can turn nasty. In this study we included a paradigm to compare central processing of scratch to itching and non-itching skin.
20 healthy subjects (10 f/10 m, mean 27,1 ± 11,3y) participated on 2 separated sessions; first psychophysical pre- and second fMRI-examination each with 2 runs: a) scratch of the untreated skin (SC-I), b) scratch after inducing itch (SC+I). Itch was applied by iontophoresis (30 sec, 1mA) of histamine to the left volar forearm. Recording started when itch intensity passes 30% of the VAS (0: no itch; 30: desire to scratch; 100: maximal conceivable itch). The left volar forearm was scratched by the experimenter using an L-shaped cupper device. Rating was continuously performed with the right hand (VAS). After each fMRI-sequences one rating was given (mean perceived itch).

MRI was done on a Siemens 3.0 T Scyra. Anatomical data: MPRAGE (1x1x1mm³) and T2-weighted brainstem set with the same orientation as EPI (36 slices). Data evaluation was done by creating a transformation matrix by manual alignment of T2-brainstem images to one selected MPRAGE. The matrix was used to align the fMRI data to the MPRAGE and to create a GLM-multi-study with predefined VOI's in BrainVoyager. Brainstem activations were identified by comparison to Duvernoy's Atlas. For the SC+I analysis periods of high itch were defined as the periods 15 seconds immediately before a scratching period (HI). In a GLM contrast were calculated between high itch period and scratching periods (CIP).
During SC-I significant activations ($p<0,05$) were found in right pontine nuclei, medial nucl. parabrachiales on bilateral and right post. hypothalamus. During SC-I activation in left locus ceruleus decreased. During HI BOLD increase were found in left pontine nuclei and decrease in PAG. During SC+I activation of the PAG significantly increased leading to a significant contrast of CIP analysis. A similar behavior was found for the right post. hypothalamus. The left nucl. ruber was activated by SC+I but not by SC-I. Significant cortical activations for itch were found in left S1, bilateral insula, S2 and BA's 40, 43 and 44.
These finding support the role of the PAG and other brainstem nuclei as key regions in modulating the pruritic input. In particular for the PAG these results show some similarities to the findings of fMRI studies on the processing of pain.

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 486.11/AA6

**Topic:** D.03. Somatosensation: Pain

**Support:** Pfizer Inc (Groton, CT) to REH

NSF GRFP

Cerephex Corporation

**Title:** Community Structure of functional brain networks during visual stimulation in chronic pain

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**Abstract:** Introduction: Fibromyalgia (FM) is a chronic centralized pain disorder in which patients experience hypersensitivity to multiple sensory stimuli. FM show increased sensitivity and brain activity in the insula, a pain processing region, during aversive visual stimulation. It is unknown whether altered network connectivity in FM also occurs during a visual task. Using graph theoretical measures, we examined changes in functional network architecture in FM during a visual stimulation task and at rest.
Methods: 40 FM patients and 19 age- and sex-matched healthy controls (HC) received visual stimulation (flashing checkboard) during fMRI. Task-specific (checkerboard and rest) correlation matrices were created for each subject, using the Conn toolbox in SPM8. Regions of interest were used based on the 264 brain regions shown to reliably produce functional network topologies at rest and during task (Powers et al, 2011). With the fully connected and weighted correlation matrices, changes in global modularity were calculated using Louvain modularity Q score for each subject for both conditions with 1000 repetitions. A consensus clustering technique was then used to define subject-level community structure for each condition. We tested whether community assignments were conserved within groups and across conditions using normalized mutual information (NMI) to quantify pairwise similarity of community structure. Higher NMI values suggest greater similarity in community structure. Independent sample t-tests were used to compare groups in each condition separately while a repeated measures General Linear Model was used to compare group by condition interactions. Statistical analyses were significant at $p < 0.05$ and determined using IBM SPSS 24.
Results: We observed no change in global modularity during visual stimulation for both FM and HC. However, NMI was significantly lower among FM patients as compared to HC during both rest and visual stimulation (both, $p < 10^{-6}$). Furthermore, there was a significant interaction between group and conditions ($p < 10^{-4}$) such that changes from rest to visual stimulation decreased NMI in HC and increased NMI in FM.
Conclusion: Despite no differences in brain network modularity, FM have more variable community structure than HC, suggesting subgroups of patient pathologies. Dynamic changes in network architecture during the visual task and rest also differed across groups suggesting that patients differ in both static and dynamic network architecture from pain free healthy controls. It remains unknown whether these differences in network architecture are consistent with other sensory stimuli either alone or in combination.

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 486.12/AA7

**Topic:** D.03. Somatosensation: Pain

**Title:** Robot guided neuronavigated rTMS in central neuropathic pain - Clinical experience and long term follow up

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**Abstract:** Background: The non-invasive brain stimulation by Repetitive Trans-cranial Magnetic Stimulation (rTMS) is increasingly used in clinical practice as a possible treatment of chronic neuropathic pain. Here we report our clinical experience on more than 1000 rTMS sessions. Eighty patients entered in an open but prospective evaluation of rTMS. All of them presented clinical symptoms typical of a unilateral central pain that was drug-resistant and lasted for at least 1 year with a moderate to severe intensity (Numerical pain scale >4/10). Methods: We used a neuronavigated rTMS to stimulate the primary motor cortex contralateral to pain with high frequencies (20Hz). A minimum of 4 sessions was proposed, each separated by 3-4 weeks. Pain was assessed by % of pain relief, Duration of Pain Relief (DPR), Neuropathic Pain Symptom Inventory (NPSI), Numerical pain Rating Score (NRS) and the Pain Relief Scale (PRS). Results: No adverse-effect was reported in the 71 patients who completed the first four sessions: pain relief was 28% in average with a mean duration of 11 days. Fifty-four patients (76%) were responders if we consider a permissive threshold of ≥10% pain-relief. With more stringent thresholds of ≥ 30% and ≥50% pain relief, the proportion of "responders" dropped to 61% (43 patients) and 45% (32 patients), respectively. Patient considered as responders kept on having rTMS sessions for 380 days on average [maximum 6 years]. After a mean number of 15 sessions per patient, cumulative effects were found on the pain relief (48%), its duration (20 days) and the prevailing NPSI sub-score (-28%). This effect was reached after 4 sessions and maintained over at least one year (15 sessions). Conclusion: These results confirm the interest and the safety of rTMS for central pain with a cumulative effect over the first 4 sessions and a stable effect after 15 sessions. The ongoing randomized controlled study will allow to precise this effect with regard to a placebo effect.

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**Poster**

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**Location:** Halls A-C

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**Program#/Poster#:** 486.13/AA8

**Topic:** D.03. Somatosensation: Pain

**Support:** the Ralph S. French Charitable Foundation Trust

NIH R01 GM107469

**Title:** Chronic *In vivo* imaging of dorsal root ganglion in a mouse model of inflammatory pain

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**Abstract:** Inflammatory pain is precipitated by an insult to the integrity of tissues, which sensitize peripheral nociceptor terminals and produce pain hypersensitivity. Intraplantar formalin injection is a model of tonic inflammatory pain, which causes a stereotypic two-phase pattern of behavioral responses, with a quiescent phase in between and a termination of the noxious stimuli responses after 45-60 minutes. Here, we developed an *in vivo* two-photon imaging technique which allows repeated imaging of dorsal root ganglion (DRG) cells in awake mice over intervals ranging from seconds to weeks. Using this technique, we found that intraplantar formalin injection substantially increases calcium activity in mouse L4 DRG sensory neurons within 1 hour, which is phase-locked with formalin-induced tonic pain behavior. This elevation of DRG neuronal activity persists for $\geq$ 6 days and gradually recovered to baseline level after 28 days. In parallel to the increased spontaneous activity of sensory neurons, formalin-injected mice

displayed non-evoked ongoing pain for at least a week in the absence of noxious stimuli. Together, our results revealed sensory neuron changes that arise during the onset and development of inflammatory pain in awake mice.

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 486.14/AA9

**Topic:** D.03. Somatosensation: Pain

**Title:** Development of a human high throughput neuronal activity assay for chronic pain

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**Abstract:** Physiologically relevant human models of chronic pain are essential to developing new therapeutics and overcome poor translation between animal studies and the clinical setting. We therefore developed a humanized screening assay with sensory neurons derived from human induced pluripotent stem cells (hiPSCs). The resulting assay can be applied in screening to identify compounds that change a disease phenotype, such as neuronal excitability, rather than the activity of specific targets. Human iPSCs were obtained from the European bank of induced stem cells (EBiSC) and a working bank of hiPSCs was produced. We differentiated the hiPSCs by dual SMAD inhibition followed by further neural commitment and patterning. Neural crest cells were cryopreserved and quality control performed to determine quality and yield of neuronal cultures. Neural crest cells were subsequently matured into functioning neurons using growth factors to induce sensory neuronal development. To determine the optimal cell density and time in culture for the assay, sensory neuronal progenitors were plated at four different densities and electric field stimulation (EFS) experiments were run after 2, 3 and 5 weeks in culture. On the day of the experiment the cells were incubated with a calcium probe and an electrode array was used to electrically excite the neurons and simultaneously an integrated imaging-based microplate reader was used to monitor the calcium response of the neurons. At the gene and protein level expression, markers for of neural crest, peripheral and sensory neurons were used (e.g. SOX10, BRN3A, *NEUROG1, OTX2*) as well as markers for pain-relevant neuronal targets such as *SCN9A*, *SCN10A*, *NTRK1*, and *TRPV1*. Using optimal settings identified during assay development, the EFS assay performance was stable and the protocols used selectively and specifically stimulated voltage-gated sodium channels. To determine whether the assay could be used for single concentration screening, it was validated by testing a LOPAC library (Sigma-Aldrich) in neurons from different batches. There was a good agreement between the replicates demonstrating assay robustness and capability to support primary screening. In

conclusion, we have identified an in vitro, human assay approach utilizing human iPSC-derived sensory neurons and a physiological stimulus that yields highly reproducible and sensitive responses in a high capacity format. This enables true phenotypic screening of compound libraries using a highly relevant stimulus (current) in human sensory neurons.

**Disclosures:** **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon AB. **A. Karlsson:** A. Employment/Salary (full or part-time):; Cellectricon AB. **D. Tams:** A. Employment/Salary (full or part-time):; Censo Biotechnologies. **A. Barnes:** A. Employment/Salary (full or part-time):; Censo Biotechnologies. **M. Karlsson:** A. Employment/Salary (full or part-time):; Cellectricon AB.

**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 486.15/AA10

**Topic:** D.03. Somatosensation: Pain

**Support:** NIH Grant NS078619

**Title:** Increasing the effectiveness of postcentral topectomy in chronic pain relief by targeted inactivation of nociresponsive area 3a

**Authors:** ***O. V. FAVOROV**[1], T. CHALLENER[1], B. L. WHITSEL[2], R. S. WATERS[3], F. P. MCGLONE[4], S. FRANCIS[5], R. SANCHEZ[5], S. ELDEGHAIDY[5]
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**Abstract:** In the mid-20th century, surgical ablations of the primary somatosensory cortex (SI), called postcentral topectomy, were used as a therapeutic means of treating patients suffering from intractable chronic pains. The outcomes varied from permanent relief of pain (approx. 60%) to temporary relief of pain (25%), and to complete ineffectiveness (15%). SI contains nociresponsive neurons in two regions: one in area 1, with properties resembling sharp, discriminative, first pain; and the second region in the anterior part of area 3a, with properties resembling burning, affective, second, slow pain. We hypothesized that permanent pain loss in postcentral topectomy was achieved when the nociresponsive part of area 3a was removed, whereas when an ablation of the postcentral gyrus failed to extend deep enough into the central sulcus to remove area 3a, the loss of pain at most was transient until area 3a recovered from indirectly induced trauma.
We tested this hypothesis by performing local SI ablations in 3 squirrel monkeys. The monkeys

were trained to obtain food reward by pulling a noxiously heated metal rod. Pull duration shows high sensitivity to rod temperature and was used as a measure of each subject's pain sensibility. In support of the hypothesis, even small ablations targeting the hand region of nociresponsive area 3a in 2 subjects significantly elevated pull durations for at least 5 months (i.e., until the subjects were euthanized), thereby indicating permanently reduced pain sensibility. In contrast, ablation of SI posterior to nociresponsive area 3a in the 3rd subject significantly reduced pull durations for at least 7 months, indicating permanently elevated pain sensibility.
Although the precise location of area 3a in the central sulcus varies extensively among humans, its nociresponsive regions can be accurately localized in any given subject by using high-resolution fMRI to image the responses evoked in the depth of the central sulcus by thermonoxious stimulation associated with chronic pain.
Once localized, the area 3a nociresponsive region can be targeted for reversible or permanent inactivation. Such precisely targeted inactivation might greatly improve the success rate of the postcentral topectomy in amelioration of pathological pain, making it a highly attractive means of treating otherwise intractable chronic pain.

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

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**Topic:** D.03. Somatosensation: Pain

**Support:** FAPESP 2012/24408-6

**Title:** Anti-NGF reverses pain behaviors and anterior cingulate cortex activation in a rat model of neuropathic pain

**Authors: *J. T. SILVA**[1], B. EVANGELISTA[1], R. VENEGA[1], D. A. SEMINOWICZ[2], M. CHACUR[1]
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**Abstract:** Introduction: Nerve growth factor (NGF) has been widely studied by the scientific community for its pro-nociceptive role in chronic pain conditions, and it is characterized as a chemical mediator responsible for the induction and maintenance of these pathologies. Chronic neuropathic pain is characterized by spontaneous burning pain accompanied by allodynia and hyperalgesia. Anti-NGF drugs have been used to reduce these symptoms in cancer pain, irritable bowel pain and osteoarthritis in both animal models and humans. However, in chronic

neuropathic pain its multiple actions are not fully understood. Methods: Male Wistar rats (200-220g, 2 months old) underwent induction of neuropathic pain by chronic constriction injury of the sciatic nerve (CCI). Sham-operated animals (Sham), which underwent the same incision, but without nerve ligation were used as control. We performed mechanical, thermal hyperalgesia and cold allodynia behavioral tests. After 14 days, we made intraplantar injections of Anti-NGF (1 and 3ug) or saline into the right hindpaw and a dose-response curve was observed. Analysis of Western blot to detect NGF and Substance P in the sensory ganglia (DRG) and spinal cord were made. In addition, neuronal activation was measured using Immunohistochemistry for Fos protein in Anterior Cingulate Cortex (ACC) and Periaqueductal gray (PAG). Results: CCI + saline demonstrated increased mechanical, thermal hyperalgesia and cold allodynia compared to Sham. After pharmacological treatment with Anti-NGF (CCI + 3ug Anti-NGF) we observed a total reversal of hyperalgesia and allodynia behaviors. Anti-NGF decreased the NGF in DRG and spinal cord after CCI, however, Substance P was decreased only in DRG. This treatment induced a reduction of neuronal activation in ACC, while it did not interfere with PAG activity. Conclusions: Our results suggest that NGF is an important factor in the induction and maintenance of neuropathic pain, since increased NGF and Substance P levels were observed in the DRG and spinal cord after injury. We also demonstrated the relevance of NGF as a therapeutic target, since Anti-NGF was able to reverse the symptoms and physiological responses in this pathology. The ACC could mediate those improvements, since it is related to emotional/motivational aspects of pain.

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

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**Program#/Poster#:** 486.17/AA12

**Topic:** D.03. Somatosensation: Pain

**Support:** National Research Foundation (NRF) of Korea (NRF-2017R1A2B3005753)

**Title:** Pain-relieving effects of rapamycin, an mTOR inhibitor, in the anterior cingulate cortex of neuropathic rats

**Authors: *S. UM**[1,2], M. TANIOKA[1,2], K. KIM[1,2], B. LEE[1,2]
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**Abstract:** The anterior cingulate cortex (ACC) is a well-known brain area recognized for its association with pain perception. According to previous studies, the ACC has been more

specifically identified for its roles in processing pain related emotional factors. Long-term potentiation (LTP) induced by abnormal sensory signaling after peripheral nerve injury is one of the main features of chronic pain in the central nervous system. Novel treatment methods for chronic pain include the termination, attenuation, or prevention of the LTP-induced excitatory transmission. Therefore, it is necessary to identify new therapeutic targets for controlling chronic pain through studies on induction and expression mechanisms of pain-related LTP. Mechanistic target of rapamycin (mammalian target of rapamycin, mTOR) is a serine-threonine protein kinase that has an important role in cell proliferation and differentiation in the nervous system. Activation of mTOR regulates protein synthesis by phosphorylating downstream factors such as eukaryotic initiation factor 4E binding protein 1 (4EBP1) and p70 ribosomal S6 protein kinase (p70S6K). Based on these studies, it can be seen that the signal transduction process associated with mTOR plays an important role in the neuroplastic changes that occur in various pain processes such as chronic pain development. In this study, we investigated the association and interactions between neuropathic pain and mTOR signaling pathway in the ACC. Under pentobarbital anesthesia, male Sprague-Dawley rats were subjected to nerve injury. The experimental animals were microinjected with rapamycin into the ACC on postoperative days (PODs) 7. Behavioral test for assessing mechanical allodynia was performed after neuropathic surgery. Inhibition of mTOR with rapamycin reduced mechanical allodynia, down-regulated the expression of phosphorylated mTOR (p-mTOR), and changed the expressions of downstream effectors, such as p70S6K and 4EBP1. These findings suggest that mTOR and its downstream pathway in the ACC may contribute in the modulation of neuropathic pain. This work was supported by the National Research Foundation (NRF) of Korea funded by the Ministry of Science, ICT, and Future Planning (NRF-2017R1A2B3005753).

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**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

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**Program#/Poster#:** 486.18/AA13

**Topic:** D.03. Somatosensation: Pain

**Support:** PI-initiated grant from Asahi Kasei Pharma

**Title:** Cortical theta predicts pain and analgesia by spinal cord stimulation

**Authors: *C. Y. SAAB**[1], S. KOYAMA[2], J. GU[3]
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**Abstract:** We previously reported that neocortical theta rhythms are correlated positively with pain, and negatively with analgesia, in awake unrestrained animals [Leblanc et al. PAIN 2014, 2016a,b]. Recently, we elucidated a thalamocortical circuitry that plays a modulatory role in controlling theta and sensory perception using optogenetic tools [Leblanc et al. Sci Rep 2017]. Here, we investigate the analgesic effects of a clinically-relevant neuromodulatory method for pain management: epidural spinal cord stimulation (SCS). Whereas SCS is widely used, its mechanisms are poorly understood, especially at a cortical level. Moreover, there is urgent need for enhancing the efficacy of non-opioid based therapies such as SCS while reducing side effects. Here, we hypothesize that conventional SCS attenuates theta recorded via EEG in Sprague Dawley rats following chronic constriction injury of the sciatic nerve. Our results show that SCS (50 Hz, 200 microsec pulse width, current amplitude below perception threshold) reverses theta with a modest effect on thermal hyperalgesia. Taken into consideration our recently reported human data [Levitt et al. Brain Res Bul 2017], we conclude that cortical theta is a valid and reliable method for the assessment of pain, analgesia and for the optimization of neuromodulation therapies including SCS

**Disclosures:** **C.Y. Saab:** 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.; Asahi Kasei Pharma. **S. Koyama:** A. Employment/Salary (full or part-time):; Asahi Kasei Pharma. **J. Gu:** A. Employment/Salary (full or part-time):; Boston Scientific.

**Poster**

**486. Thalamic and Cortical Pain Processing and Treatment**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 486.19/AA14

**Topic:** D.03. Somatosensation: Pain

**Support:** Asahi Kasei Pharma

**Title:** Cortical theta predicts pain, analgesia and side effects of high dose analgesia

**Authors: *S. KOYAMA**[1], B. W. LEBLANC[2], C. Y. SAAB[2]
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**Abstract:** We previously reported that neocortical theta rhythms correlate positively with pain, and negatively with analgesia in animals [Leblanc et al. PAIN 2014, 2016a,b]. Here, we record EEG to further compare the sensitivity of theta versus behavioral measures in detecting sub-therapeutic doses of pregabalin (PGB), and potential side effects at high doses in awake, unrestrained Sprague Dawley rats following chronic constriction injury of the sciatic nerve. Our

results show that PGB reverses thermal hyperalgesia, invariably, at sub-therapeutic, therapeutic and extra-therapeutic doses, whereas theta predicts a therapeutic dose in accordance with clinical data. Moreover, extra-therapeutic doses of PGB induces a paradoxical increase in theta and theta/gamma ratio, suggesting possible detection of side effects such as drowsiness. Taken into consideration our recently reported data in humans [Levitt et al. Brain Res Bul 2017], we conclude that EEG rhythms in the theta and gamma bands are valid correlates of pain, analgesia and side effects of high-dose analgesia.

**Disclosures:** **S. Koyama:** A. Employment/Salary (full or part-time):; Asahi Kasei Pharma. **B.W. LeBlanc:** A. Employment/Salary (full or part-time):; Rhode Island Hospital & Brown University. **C.Y. Saab:** A. Employment/Salary (full or part-time):; Rhode Island Hospital & Brown University.

**Poster**

**487. Somatosensory System Plasticity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 487.01/AA15

**Topic:** D.04. Somatosensation: Touch

**Title:** Automated sensory association training reveals input-specific plastciity in mouse barrel cortex

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**Abstract:** Sensory experience can cause long-lasting alterations to the activity and circuitry of the neocortex, but the cell-type and pathway-specific sequence of events underlying these changes is unknown. This is especially true for plasticity driven by naturalistic stimuli which may not follow the principles of cortical rewiring established for coarse manipulations like sensory deprivation. Here we define the characteristic sequence of cell-type and pathway-specific changes that occur across the cortical column during sensory association training in the mouse barrel cortex. Using an automated, home-cage training chamber that couples whisker deflection to a water reward, we characterized neural responses following activation of VPM and POm, the two main thalamic inputs to the cortex, during different phases of learning. Optogenetic stimulation of thalamic afferents revealed pathway- and cell-type specific changes in evoked spike output, assessed by patch-clamp recordings in acute brain slices. After just 24 hours of sensory training, POm afferent stimulation drove significantly increased evoked firing in layer 2 and layer 5 pyramidal neurons. Elevated spiking activity was present both during the stimulation window and during the recurrent intracortical network activity that persisted for

seconds after stimulus cessation. In contrast, spiking activity evoked by stimulation of VPM afferents was unchanged by sensory association training. These data indicate that sensory association training drives rapid and specific enhancements in the POm-recipient circuitry of the somatosensory cortex. The sequence of these changes across different layers and cell types reveals principles for the reorganization of neocortical circuits associated with learning and also suggests a possible role for second-order thalamic nuclei in facilitating cortical plasticity.

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**Poster**

**487. Somatosensory System Plasticity**

**Location:** Halls A-C

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**Topic:** D.04. Somatosensation: Touch

**Support:** BFU2012-39960 MINECO/FEDER

BFU2015-66941R MINECO/FEDER

**Title:** Sensory input-dependent structural plasticity of primary afferents in the trigeminal system of the adult rat

**Authors: *J. FERNÁNDEZ-MONTOYA**[1], Y. B. MARTIN[2], P. NEGREDO[3], C. AVENDAÑO[3]
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**Abstract:** Lasting modifications of sensory input induce structural and functional changes that have been extensively studied in higher levels of the central nervous system. The participation in these plastic phenomena of structures involved in the early stages of sensory processing has been largely ignored. In our group we have demonstrated that sustained alterations of sensory input in the vibrissal system in adult rats induce morphometric changes in the dendritic arbors of second order neurons in the principal (Pr5) and the caudal (Sp5c) trigeminal nuclei. More recently, we also showed that the trigeminal ganglion, where primary sensory neurons reside, displays marked expression changes in genes and proteins involved in glutamatergic neurotransmission following sensory input manipulation. Here, we examined whether the same manipulations are capable to structurally modify central terminal arbors of primary sensory neurons. We have performed injections in a single deep vibrissal nerve (DVN) of a mixture of cholera-toxin B (CTB) and isolectin B4 (IB4), tracers for myelinated and unmyelinated fibers respectively, in three groups

of young adult male rats: controls, rats chronically deprived of haptic touch by repeated unilateral whisker trimming, and rats exposed to environmental enrichment for the same period of time. The central terminations of these axons in the trigeminal complex were studied by immunostaining and stereology. The regional and laminar pattern of terminal arborizations in the trigeminal nuclei of the brainstem did not show gross changes after sensory input modification. However, there were significant and widespread increases in the number and size of CTB-labeled varicosities in the enriched condition, and more modest increases in the whisker trimming condition, save for a prominent expansion in both parameters in laminae III-IV of Sp5c. No obvious changes were detected in IB4-labeled terminals in laminae I-II. These results show that a prolonged exposure to changes in sensory input without any neural damage is capable of inducing structural changes in terminals of primary afferents in mature animals, and highlight the importance of peripheral structures as the presumed earliest players in sensory experience-dependent plasticity.

**Disclosures: J. Fernández-Montoya:** None. **Y.B. Martin:** None. **P. Negredo:** None. **C. Avendaño:** None.

**Poster**

**487. Somatosensory System Plasticity**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 487.03/AA17

**Topic:** D.04. Somatosensation: Touch

**Support:** NIGMS 1SC3GM122657 - 01

**Title:** The effect of sensory deprivation on vasculature organization in the mouse barrel cortex

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**Abstract:** Whisker trimming is a commonly studied form of sensory deprivation in mice, whose prominent facial whiskers are represented in a one-to-one fashion in the layer four barrel cortex. Following one month of whisker trimming induced deprivation neural morphology is altered; how deprivation impacts the associated vasculature is unknown. Whisker trimming was performed from birth to post-natal day 30, by clipping the mystacial whiskers every other day, followed by transcardial perfusion and fixation. Brains were then sliced in the coronal plane and their neural vasculature was revealed using Lycopersicon esculentum lectin conjugated to Texas Red. Image stacks were obtained using a confocal microscope; NeuroLucida software was used to reconstruct a three-dimensional representation of the neural vasculature that was then quantified. Results showed that trimming affected vasculature distribution on several scales of

measurement. Trimmed animals exhibited significantly decreased overall vascular length, surface area, and volume and less torturous vessels with fewer terminal endings. Similar to neural structures the neural vasculature is influenced by afferent sensory inputs via the animals' whiskers.

**Disclosures: E. Yakubova:** None. **F.A. Iskhakova:** None. **J.C. Brumberg:** A. Employment/Salary (full or part-time):; The Graduate Center, CUNY.

**Poster**

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**Topic:** D.04. Somatosensation: Touch

**Support:** NINDS Competitive Postdoctoral Fellowship

**Title:** Unilateral loss of whisker sensation leads to synaptic remodeling across the corpus callosum

**Authors: *E. R. PETRUS**, A. P. KORETSKY
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**Abstract:** The corpus callosum (CC) is a major fiber bundle which links the two brain hemispheres, and is critical for bilateral integration of senses and coordination of motor output (Berlucchi et al. 1995). The CC plays a complex role when coordinating homotopic contralateral cortical areas, with a balance of inhibitory and excitatory inputs enabling this integration to occur (Bloom and Hynd 2005). For bilateral senses such as the somatosensory whisker system in rodents, the loss of one whisker set via infraorbital nerve transection (ION) produces changes in the spared thalamo-cortical pathway, but also inappropriate response of the deprived somatosensory barrel cortex (S1BC) to ipsilateral intact whisker stimulation (Yu et al. 2012). In addition, unilateral ablation of the spared S1BC produces profound cortical reorganization in the deprived S1BC and neighboring nose and forepaw areas (Yu et al. 2014). This indicates that the CC may mediate circuit reorganization in the deprived S1BC in adult rodents.
Our work seeks to identify the synaptic targets of the CC from the spared to deprived S1BC which drives this cortical rewiring. We used channel rhodopsin to activate the spared S1BC and recorded responses in principal cells in deprived S1BC in 3 month old mice. We have identified layer 5 neurons as the major remodeled targets of the CC, which experience a doubling of AMPA receptor mediated response size in ION vs. controls. This potentiation is associated with occlusion of LTP which normally occurs along this pathway. These results support the hypothesis that even fully mature circuits can undergo synaptic plasticity. Further characterization of the cells and the synaptic basis for these changes in adults will be helpful for

understanding how the brain rewires after injury due to stroke, traumatic brain injury or loss of peripheral sensation due to the loss of limbs or nerve damage. Future work will study how the potentiation of these inputs leads to effects on cortical map plasticity.

**Disclosures: E.R. Petrus:** None. **A.P. Koretsky:** None.

**Poster**

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**Title:** Ipsilateral responsiveness in area 3b with and without treatment after dorsal column spinal cord injury in New World monkeys

**Authors: *J. L. REED**[1], H.-X. QI[1], C.-C. LIAO[1], M. P. SARAF[1], M. M. PAKULSKA[2], M. S. SHOICHET[2], J. H. KAAS[1]
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**Abstract:** Lesions of the spinal cord dorsal columns produce a permanent loss of primary afferents to the brainstem cuneate nucleus, depriving cortex of activating inputs. Months after unilateral lesions to the cervical dorsal columns, primary somatosensory cortex (area 3b) reactivates and hand use improves. These recoveries are incomplete; therefore, we investigated a treatment with chondroitinase ABC (ChABC) using an affinity release hydrogel (Pakulska et al. 2015). ChABC digests extracellular chondroitin sulfate proteoglycans to reduce barriers that prevent axons from growing to their targets. Here we focus on how the ChABC hydrogel delivered at and around the spinal cord lesion affected responsiveness to touch on the ipsilateral hand. Neurons in the area 3b hand representation do not appear to respond to ipsilateral stimulation, but stimulating both hands tends to suppress activity in 3b. We hypothesized that reorganization after unilateral dorsal column lesion (DCL) allows some inputs from the ipsilateral hand to activate deprived cortex. We further hypothesized that ChABC hydrogel treatment would promote normal cortical reactivation and possibly eliminate ipsilateral responses. Subjects were New World owl monkeys (*Aotus*) and squirrel monkeys (*Saimiri*). We

recorded responses to tactile stimulation using implanted multi-electrode arrays in the 3b hand representation of intact monkeys (N = 5) and monkeys 5-12 weeks after unilateral DCL, with (N = 4) or without ChABC treatment (N = 4). ChABC did not reactivate all neurons in area 3b, but those that reactivated responded to touch on the contralateral hand with properties that did not differ from those of intact monkeys. Responses to the ipsilateral hand were detected in 3 out of 4 ChABC cases (15 responses). In DCL cases without ChABC, 17 responses to the ipsilateral hand were detected. Peak response magnitudes were similar in all three groups to ipsilateral and contralateral stimulation, but contralateral response latencies in the ChABC group were faster than those in the DCL group. In the ChABC group, ipsilateral response latencies were slower (~30ms) than contralateral response latencies (~18ms). In the DCL group, ipsilateral and contralateral latencies were similar (~29ms, ~33ms, respectively). Overall, within the 12-week period, the ChABC treatment did not eliminate ipsilateral responsiveness, despite contralateral response properties within normal ranges. The sources of ipsilateral hand responses in area 3b are uncertain, but they seem to be more prevalent in monkeys after DCL, with and without the ChABC treatment.

**Disclosures:** **J.L. Reed:** None. **H. Qi:** None. **C. Liao:** None. **M.P. Saraf:** None. **M.M. Pakulska:** None. **M.S. Shoichet:** None. **J.H. Kaas:** None.

**Poster**

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**Topic:** D.04. Somatosensation: Touch

**Support:** NIH grant NS16446

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Craig H. Neilsen Foundation

**Title:** Intracortical connections of area 3b after cortical treatment with chondroitinase ABC in squirrel monkeys with a dorsal column lesion

**Authors: *C.-C. LIAO**, J. L. REED, H.-X. QI, M. P. SARAF, J. H. KAAS
Dept. of Psychology, Vanderbilt Univ., Nashville, TN

**Abstract:** After injuries of the tactile dorsal column afferents in cervical spinal cord, the primary somatosensory hand cortex in the contralateral hemisphere is inactivated, and dexterous hand use is impaired. Over weeks to months, the deafferented neurons become responsive to touch on the hand, and hand use recovers. Previous studies have revealed that chondroitinase ABC (chABC) treatment at subcortical levels could increase the reactivation of cortex after spinal cord injuries.

Here we test whether chABC treatment in cortex promotes the cortical reactivation by increasing the growth of intracortical connections. A unilateral dorsal column lesion (DCL) was made at the C5 level in one squirrel monkey (*Saimiri boliviensis*). The lesion interrupted the inputs from digits 3 to 5 and part of the digit 2, but spared the inputs from the digit 1. Immediately after the DCL, chABC was locally injected at the rostral and caudal borders of area 3b, where hand cortex adjoins the forelimb region medially and the face region laterally (4 sites). After 2 months, biotinylated dextran amine (BDA) and fluoro-ruby (FR) were injected into the electrophysiologically identified forelimb and digit 1 representations in area 3b, respectively. We mapped the hand region in area 3b by microelectrode multiunit recordings to evaluate the postlesion cortical reactivation. The results were compared to the data from one control squirrel monkey (*Saimiri boliviensis*). We found that neurons in the most medial region of the hand cortex remained unresponsive after DCL, but neurons in the lateral region responded to touch on digits 1 and 2, occasionally to digit 4, multiple digits, or larger areas involving the hand and forelimb. Nevertheless, the organization of intracortical connections after the DCL resembled the normal pattern. BDA-labeled neurons and terminals were primarily distributed in the forelimb region in area 3b, slightly spreading medially into the hand region. Yet, their distribution did not overlap the newly-formed forelimb representations in the deafferented hand cortex. Populations of BDA-labeled neurons and terminals were also present in the expected locations of forelimb regions in areas 3a, 1, and 2, and primary motor cortex. We also found scattered BDA-labeled neurons and terminals in the supplementary somatosensory cortex, parietal ventral, secondary somatosensory cortex, ventral somatosensory area, and the retroinsular area. Taken together, our preliminary data suggest that with the acute chABC treatment in the cortex, most of the expected intracortical connections of area 3b neurons remain intact in the monkey after the DCL, and the treatment did not greatly alter the connections.

**Disclosures: C. Liao:** None. **J.L. Reed:** None. **H. Qi:** None. **M.P. Saraf:** None. **J.H. Kaas:** None.

**Poster**

**487. Somatosensory System Plasticity**

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**Program#/Poster#:** 487.07/AA21

**Topic:** D.04. Somatosensation: Touch

**Support:** UTHSC Research Foundation

**Title:** Rapid remapping of hand-to-face representation in primary somatosensory SI cortex in rat following brachial plexus nerve cut and brachial plexus anesthesia

**Authors: *A. L. CURRY**[1], V. PELLICER MORATA[2], J. W. TSAO[2], O. V. FAVOROV[3], R. S. WATERS[4]

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**Abstract:** Introduction: In some patients, brachial plexus (BP) injury can result in phantom limb pain (PLP) and phantom limb sensation (PLS) in the deafferented limb immediately after the injury. BP injury may also result in remapping the deafferented forelimb onto the face, examined 6 months after injury, but whether remapping also occurs in temporal register with PLP and PLS is unknown. Here, we examined this temporal question using an animal model employing forepaw and lower jaw (LJ) representations in the rat barrel field in primary somatosensory (SI) cortex.
Methods: In adult Sprague-Dawley rats, anesthetized with Ketamine/Xylazine (100-mg/kg), the BP nerve was cut (BPnc) or anesthetized (BPA) using lidocaine. Extracellular recordings and mechanical and electrical stimulation were used to map forepaw and LJ [chin, lip, lower jaw] representations and the boundary between the representations in SI cortex immediately before and within 1 hour after BPA and BPnc.
Results: Neurons in forepaw and LJ representations received input only from their respective peripheral locations. Following BPnc and BPA, neurons in the deafferented forepaw SI cortex immediately adjacent to the LJ representation became responsive within 1 hr to new input from the lower jaw. In contrast, neurons in non-adjacent forepaw sites remained unresponsive. Ablation of the LJ SI cortex immediately adjacent to the forepaw SI cortex abolished the new LJ responses in forepaw cortex. BPnc produced more robust remapping than did BPA.
Conclusion: Rapid forepaw-to-face remapping in the border region of rat forepaw SI cortex occurs following BPA and BPnc. We propose that new LJ input is very likely relayed from adjacent LJ barrel field. Our finding may assist in identifying cortical and subcortical mechanisms relevant to remapping human cortex subsequent to limb deafferentation.

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**Poster**

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**Topic:** D.04. Somatosensation: Touch

**Support:** NSF EPSCoR Grant 1632849

NIH GM104941

**Title:** Motor and somatosensory reorganization in a patient with a somatosensory lesion

**Authors: Y. LIU**[1], O. FASEYITAN[2], H. B. COSLETT[2], *J. MEDINA[1]
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**Abstract:** How do sensory and motor networks change after damage to somatosensory cortex? Although cortical plasticity after somatosensory damage has been studied extensively in animal models, little research has been done in humans examining the behavioral and neural correlates of primary somatosensory cortex (S1) damage in humans. We tested an individual who, due to a stroke, suffered a unique lesion with extensive damage to left S1 and posterior parietal cortex, while leaving left primary motor cortex (M1) and subcortical structures intact. First, a sensorimotor behavioral battery revealed the expected sensory deficits on the contralesional limb, including impaired tactile localization, finger identification, and proprioception. Although his tactile perception was diminished, he could still feel tactile stimuli of moderate intensity. Given the extensive damage to the traditional hand area of S1, we then used functional neuroimaging to examine what brain regions represented touch after stroke. To do this, we presented either hand with tactile stimulation (brush strokes) using a blocked fMRI design. As expected, we found activation in right S1 when stimulating the ipsilesional (left) hand. However, when stimulating the contralesional (right) hand, we found activation in left M1, providing evidence for somatosensory reorganization into intact cortex neighboring the lesion site. Given this reorganization into motor cortex, we then examined what brain regions were active for hand movement (opening and closing the hand without seeing the hand) versus rest in a second imaging session. Movement of either the left or right hand resulted in significant activation in two areas - bilateral putamen and right area MT. Interestingly, there was a relatively limited amount of cortical activation in sensorimotor cortex for hand movement versus rest. These findings provide evidence for reorganization of somatosensory processing into neighboring motor cortex. Furthermore, with limited sensory feedback, individuals may strongly rely on areas outside of sensorimotor cortex for movement control and execution.

**Disclosures: Y. Liu:** None. **O. Faseyitan:** None. **H.B. Coslett:** None. **J. Medina:** None.

**Poster**

**487. Somatosensory System Plasticity**

**Location:** Halls A-C

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**Topic:** D.04. Somatosensation: Touch

**Support:** German Research Foundation (DFG), SFB 874

**Title:** Neurofeedback-induced modulation of somatosensory alpha power controls subsequent tactile learning

**Authors: *M. BRICKWEDDE**[1,2], H. R. DINSE[1,2]
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**Abstract:** Oscillatory alpha power is believed to occupy an inhibitory function which gates neuronal resources (Klimesch et al., 1999, Cogn Brain Res). To obtain information about processes controlling learning variability, we have previously shown that baseline power of somatosensory alpha recorded before tactile learning predicted 36 % of the learning variance (Freyer et al. 2013, J Neurosci). Here we took advantage of these findings by aiming at purposefully altering somatosensory alpha power to systematically manipulate subsequent learning success in human participants.
A total of 74 participants were randomly assigned to three groups. The first group (alpha up) trained to increase somatosensory alpha power for 20 min using a Thera Prax® Mobile neurofeedback system. The second group (alpha down) trained to decrease somatosensory alpha power under otherwise identical conditions. The control group performed no neurofeedback training. We induced perceptual learning with high frequency LTP-like repetitive sensory stimulation (RSS) applied to the right fingertip. Before and after RSS, we assessed the tactile spatial discrimination ability as marker of plastic changes. RSS was applied for 20 min on the second day immediately after a second session of 15 min of neurofeedback training. We could show that the alpha up group strongly increased their somatosensory alpha power, while the alpha down group showed a slight decrease. As a result of neurofeedback training, the alpha up group showed significantly higher tactile learning gains than controls. In contrast, in the alpha down group tactile learning was suppressed. Individually, the amount of somatosensory alpha power gain correlated with the subsequent learning success in the tactile spatial discrimination task.
Our results suggest that high levels of alpha power create an optimal state for subsequent stimulation based perceptual learning. We currently investigate whether altered alpha power affects the efficacy of sensory processing, or the learning processes itself, or both. Since RSS is a promising intervention in the rehabilitation of stroke patients, a combination with neurofeedback training could be utilized to further enhance the rehabilitation process.

**Disclosures: M. Brickwedde:** None. **H.R. Dinse:** None.

**Poster**

**487. Somatosensory System Plasticity**

**Location:** Halls A-C

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**Program#/Poster#:** 487.10/AA24

**Topic:** D.04. Somatosensation: Touch

**Title:** Responses to outgrowing / young and old whiskers in layer 4 barrels of rat somatosensory cortex

**Authors: *E. MAIER**, M. BRECHT
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**Abstract:** Rodents touch objects with their whiskers in order to make sense of the external world. Similar to other hair, whiskers adhere to a cycle that is characterized by different phases whereby a young whisker grows out of the same follicle and the old whisker falls out when the young one reaches a certain length (Ibrahim et al. 1975). Responses of single neurons in the barrel cortex to external stimulation of the whiskers have been studied extensively during the past decades both in anesthetized and awake animals. To our knowledge, however, no study has focused on stimuli applied separately to the young and the old whisker respectively. Moreover, although anatomical examinations of the follicle during whisker regrowth have been described (Kim et al. 2010), the topographic relationship between the young and old whisker has not been addressed. In this study we report a robust and stereotypic topographic relationship between young and old whiskers, with the base of the young whisker mostly being located rostro-ventrally of the old one. In order to assess how young and old whiskers are represented by the activity of neurons at different locations within the barrel, we recorded and identified layer 4 neurons in the barrel cortex of anesthetized rats with juxtacellular electrophysiological experiments. The young and old principle whiskers were deflected in different angular directions. We find that for the majority of layer 4 neurons (12/15) the total spike count response appears to be larger for deflections of the old whisker. The few neurons (3/15) with higher total spike count after young whisker stimulation were located at the caudal proportion of the barrels. Neurons that responded to both whiskers showed similar angular tuning. Our findings suggest a dominance of the old whisker in sensory responses and a matching of angular properties of old and young whisker responses.

**Disclosures:** **E. Maier:** None. **M. Brecht:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

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NSFC Grant 20151311567

**Title:** Distinct maturational trajectory of temporal processing in thalamocortical recipient layers 4 and 5

**Authors: *F. XIE**[1], L. YOU[2], D. CAI[3], M. LIU[2], Y. YUE[2], Y. WANG[2], K. YUAN[4]
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**Abstract:** As in other primary sensory cortices, both layer 4 (L4) and layer 5 (L5) of the primary auditory cortex (A1) receive substantial thalamic inputs. Temporal processing in L4 of both developing and adult A1 has been extensively studied. However, conclusions about temporal response properties in L5 compared to L4 are still controversial. Furthermore, the maturational process of temporal processing in L5 remains unknown. Using loose-patch recordings in-vivo, we found that the temporal response resolution of L5 neurons in the adult rat A1 is not significantly different from that of L4 neurons. However, very interestingly, L5 neurons exhibit superior stimulus-following ability immediately after hearing onset, in contrast to the poor temporal responses of L4 neurons. In fact, no significance difference in temporal processing was observed between L5 neurons in the developing and adult A1. In-vivo whole-cell voltage-clamp recordings showed that L4 and L5 neurons in the developing A1 are not significantly different from each other in terms of both resting membrane potential and the adaptation of both excitatory and inhibitory inputs, although L5 neurons are more depolarized and the adaptation of inhibition is stronger in the adult A1. However, the duration of inhibitory input to L5 neurons is remarkably shorter than that to L4 neurons in the developing A1, while they are similarly short in adults. Moreover, the difference in inhibitory duration between L5 of developing and adult A1 is only a fraction of that between L4 of the two age groups. Repetitive stimulation does not evoke summation of inhibition in L5, keeping the classical temporal sequence between excitation and inhibition. These results have several implications. First, they further confirmed that the duration of inhibition plays a critical role in setting the pace for the maturation of cortical temporal processing. Second, they suggest that the inhibitory circuits in L4 and L5 are distinct, at least partly underlying the difference in the developmental trajectory of functional properties. Last but not least, they support the notion that although both L4 and L5 are thalamocortical recipient layers, they may represent two separate systems subserving distinct functions.

**Disclosures: F. Xie:** None. **L. You:** None. **D. Cai:** None. **M. Liu:** None. **Y. Yue:** None. **Y. Wang:** None. **K. Yuan:** None.

**Poster**

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**Topic:** D.06. Audition

**Support:** Czech Science Foundation 16-09086J

**Title:** Behavioral assessment of sound intensity discrimination in rats exposed to noise as juveniles

**Authors: *D. SUTA**[1], N. RYBALKO[2], T.-W. CHIU[3], J. SYKA[2]
[1]Dept. of Cognitive Systems and Neurosciences, CIIRC Czech Tech. Univ., Prague, Czech Republic; [2]Dept. of Auditory Neurosci., Inst. of Exptl. Medicine, Czech Acad. of Sci., Prague, Czech Republic; [3]Dept of Biol. Sci. and Technology, NCTU, Hsinchu, Taiwan

**Abstract:** Several studies demonstrated that brief noise exposure in rat pups can result in altered behavioral responses to sounds in adulthood even in individuals with normal hearing thresholds. Rybalko et al. (Physiol Behav 102: 453, 2011) reported anomalies in intensity coding and loudness perception in adult rats exposed as juveniles. In this study we tested sound intensity discrimination in rats exposed to noise as juveniles and compared them with control animals. Behavioral testing was performed by a modified method of the prepulse inhibition of the acoustic startle response. Measurement of prepulse inhibition of the acoustic startle response is a behavioral method that has been frequently used for efficient and accurate assessment of both simple and complex acoustic discrimination in rodents. During each session, a background tone of a constant frequency and intensity was continuously presented to the animal. Intensity of the background tone was either increased or decreased for a short period preceding presentation of the startle stimulus; this change in sound intensity served as the prepulse stimulus. Presentation of the prepulse (i.e. a modulation of the sound intensity) systematically reduced startle response - the magnitude of startle response was generally smaller (inhibited) than that without intensity modulation. The inhibition of startle response was observed for prepulses with a positive as well as negative difference in sound intensity. In summary, our results illustrate that measurement of the startle response can be successfully applied for evaluation of intensity discrimination at moderate sound intensities in control as well as noise-exposed animals.

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**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

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NSFC Grant 20151311567

**Title:** A critical role of inhibition in temporal processing maturation in the primary auditory cortex

**Authors: *K. YUAN**[1], D. CAI[2], M. LIU[3], F. XIE[3], L. YOU[3], Y. WANG[3], Y. YUE[3]
[1]Tsinghua Univ., Beijing City, China; [2]Biomed. Engineering,School of Med., [3]Biomed. Engineering, Sch. of Med., Tsinghua Univ., Beijing, China

**Abstract:** Faithful representation of sound envelopes in primary auditory cortex (A1) is vital for temporal processing and perception of natural sounds. However, the emergence of cortical temporal processing mechanisms during development remains poorly understood. Although cortical inhibition has been proposed to play an important role in this process, direct *in vivo* evidence has been lacking. Using loose-patch recordings in rat A1 immediately after hearing onset, we found that stimulus-following ability in fast-spiking (FS) neurons was significantly better than in regular-spiking (RS) neurons. *In vivo* whole-cell recordings of RS neurons revealed that inhibition in the developing A1 demonstrated much weaker adaptation to repetitive stimuli than in adult A1. Furthermore, inhibitory synaptic inputs were of longer duration than observed *in vitro* and in adults. Early in development, overlap of the prolonged inhibition evoked by two closely following stimuli disrupted the classical temporal sequence between excitation and inhibition, resulting in slower following capacity. During maturation, inhibitory duration gradually shortened accompanied by an improving temporal following ability of RS neurons. Both inhibitory duration and stimulus-following ability demonstrated exposure-based plasticity. These results demonstrate the role of inhibition in setting the pace for experience-dependent maturation of temporal processing in the auditory cortex.

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**Poster**

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**Topic:** D.06. Audition

**Support:** NSF Grant 1552946

**Title:** Adaptive granger causality analysis reveals functional network dynamics underlying attentive behavior at neuronal scale

**Authors: *A. SHEIKHATTAR**[1], S. MIRAN[1], J. LIU[2], J. B. FRITZ[3], S. A. SHAMMA[1,3], P. O. KANOLD[2,3], B. BABADI[1,3]

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**Abstract:** Growing evidence in experimental and computational neuroscience suggests that higher order brain function emerges from causal interaction and collective cooperation of functionally inter-connected networks of neurons. These functional networks are highly dynamic and comprise sparse patterns of connectivity, which enable the brain to robustly adapt to rapid changes in the environment. Existing methods for inferring causal interactions in a network of neurons often provide static measures of causality. Moreover, most of these methods are restricted to models with linear Gaussian statistics, and do not take into account the sparsity of the underlying functional network structure. They are therefore not well-suited to neuronal spiking data with rapid task-dependent dynamics, binary statistics, and sparse functional dependencies. To address these challenges, we develop a novel inference framework through integrating Granger causality analysis, adaptive filtering, compressed sensing, point process modeling and high-dimensional statistics. We propose an adaptive Granger causality (AGC) measure, with embedded sparsity and dynamic features, specifically tailored for neuronal spiking observations. We derive efficient estimation algorithms and precise statistical inference procedures for the AGC measure, which allow us to detect and assess the statistical significance of the functional network dynamics in a neuronal ensemble. Application of our method to two-photon recordings from the mouse auditory cortex reveals the highly sparse and dynamic structure of functional network interactions underlying spontaneous activity at unprecedented spatiotemporal resolution. Our analysis of simultaneous electrophysiology recordings from the ferret primary auditory (A1) and prefrontal cortices (PFC) under auditory task conditions suggests evidence for the role of rapid task-relevant changes in the functional network dynamics within and across these two cortical regions in robust attentive behavior at the neuronal scale.

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**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 488.05/AA29

**Topic:** D.06. Audition

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**Title:** Effect of focal attention on the cortical entrainment of the speech envelope

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**Abstract:** Recent progress in decoding brain responses to a speech stimulus has allowed developing novel measures for speech intelligibility based solely on electroencephalography (EEG). However, the cortical entrainment to speech varies over time independently of the intelligibility, reducing its applicability as an objective measure of speech intelligibility. We here hypothesized that periods with low-attention to the speech signal are associated with a lower cortical entrainment to speech, while higher levels of attention produces higher cortical entrainment. To evaluate this hypothesis, we presented running speech from a narrated story binaurally to fifteen normal hearing subjects. The reconstructed speech envelope was decoded from low-frequency EEG signals (0.5-4Hz; 64 electrodes) using a linear regression model (integration window: 0-250 ms) and the cortical entrainment was then computed as the correlation between presented and reconstructed speech envelope. In parallel, brain markers of focal attention were also extracted for each recording electrode using normalized spectral entropy. Finally, Spearman's correlation between each channel's spectral entropy and cortical entrainment over time was computed in the frontal area. Average cortical entrainment was 0.21 ± 0.08. Interestingly two participants presented lower cortical entrainment (respectively, 0.15 ± 0.06 and 0.14 ± 0.09) than the others (range: 0.20-0.27). These participants presented the highest correlation (respectively, 0.28 and 0.30) between the frontal entropy and the cortical entrainment (average: 0.03 ± 0.17) over time, suggesting a modulation of cortical entrainment with attention. Selection of periods with highest entropy (threshold was set as the 75th percentile) allowed to increase cortical entrainment to 0.18 (increase: 0.03) and 0.20 (increase: 0.06) respectively. Other individuals showed no difference in average in the cortical entrainment using only high frontal entropy periods. This study suggests that an increase in focal attention could induce an increase in the cortical entrainment to speech independently of the level of speech intelligibility. We here proposed to track and correct the effect of attention using spectral entropy-based markers in the frontal area. This could provide objective measures of speech intelligibility in clinical routine and open doors to automatic cochlear implant parameter adaptation without the intervention of a clinical expert.

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**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

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DOD Grant W81XWH-15-1-0435

**Title:** Auditory brainstem response changes following repeated mild closed head injury

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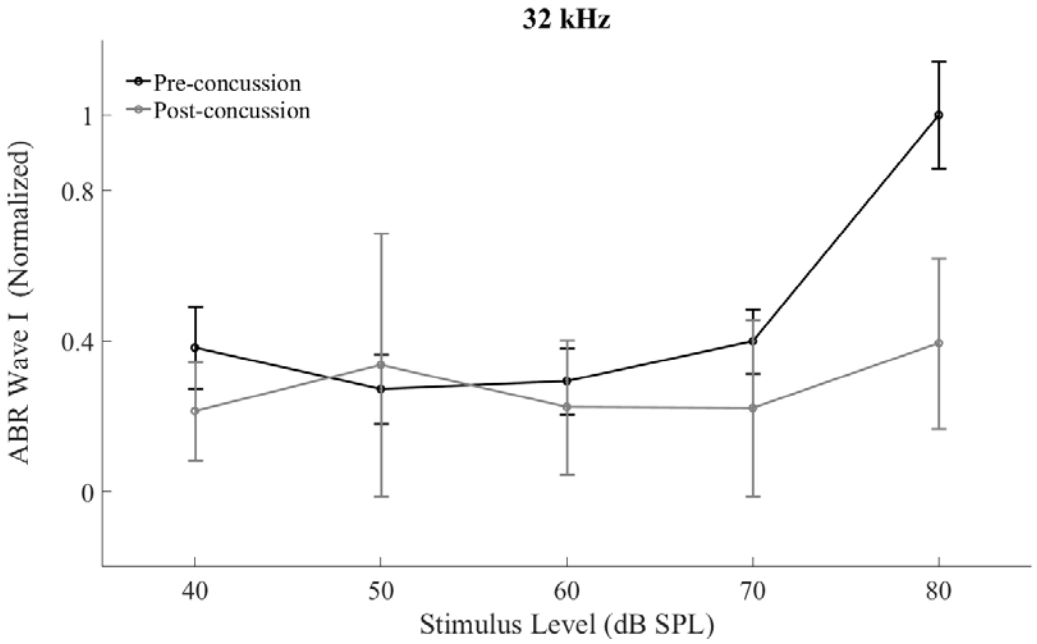
**Abstract: Background**: Sensorineural hearing loss is primarily associated with cochlear hair cell loss followed by cochlear nerve degeneration. Recent studies have revealed that "synaptopathic" noise exposure can result in primary auditory neurodegeneration and "hidden hearing loss." This phenomenon results in dramatically diminished auditory brainstem response (ABR) wave 1 amplitude in animals subjected to noise trauma that only created a temporary threshold shift. This phenomenon may also contribute to tinnitus, hyperacusis, difficulty hearing in noisy environments, and other auditory processing anomalies. In addition to noise exposure, closed head injury (CHI) is known to be associated with tinnitus, often despite unchanged hearing thresholds. The mechanism by which TBI affects the auditory system is poorly understood. We aim to investigate the impact of repeated mild CHI (rmCHI) on the auditory system.
**Methods**: Baseline ABR thresholds were obtained in seven 10-week old litter-mate male wild-type C57/Bl6 mice. Wave I-V amplitudes and latencies were measured at 8, 16, 24, and 32 kHz. Stimuli were presented at 40, 50, 60, 70, and 80 dB SPL. A single standardized head injury (speed: 5 m/s, depth: 1 mm, dwell time: 500 ms) was delivered to each anesthetized mouse daily for 5 days with a TBI-0310 Impactor, and ABRs were re-measured.
**Results**: Pre- and post-concussion ABR thresholds were within 5 dB at lower frequencies, while there was a 10 dB threshold shift at 32 kHz. While there were no significant changes in suprathreshold amplitudes at the lower frequencies measured, a 60% decrease in amplitude (SE: 0.15) and .28 ms latency shift (SE: 0.11) in wave 1 at 32 kHz was observed.
**Conclusion**: Our results show that rmCHI resulted in reduced ABR wave I amplitude and increased latency at the frequency exhibiting a greater threshold shift and may be suggestive of auditory synaptopathy. Ongoing investigation will be directed at establishing rmCHI levels that

result in temporary and permanent threshold shifts and determining their short- and long-term impact on auditory neurophysiology.

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**Poster**

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**Support:** R01 DC009836

**Title:** Data-driven segmentation of mouse auditory cortical fields based on mesoscale optical Ca2+ imaging

**Authors:** ***S. A. ROMERO PINTO**[1], D. B. POLLEY[2], A. HIGHT[1], J. RESNIK[2]
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**Abstract:** Microelectrode mapping studies have identified two tonotopically organized fields in the mouse auditory cortex (ACtx), the primary ACtx (A1) and the anterior auditory field (AAF),

surrounded by a secondary auditory field (A2), a dorsoposterior field (DP) and the insular auditory field (IAF). Interest in cortical organization at “mesoscale” resolution (i.e., roughly 50 microns) has been revived thanks to optical imaging of genetically encoded calcium indicators (GECIs) that offer a higher signal-to-noise ratio than intrinsic signals, flavoproteins or bulk-loaded calcium indicators. Widefield epifluorescence imaging of GECIs in mouse ACtx has confirmed the basic organization published in earlier microelectrode mapping studies, with two unexplained discrepancies: First, a “dead” zone between A1 and AAF that does not respond to tones (but may instead respond to more complex sounds such as FM sweeps). Second, high-frequency regions lateral to the principal tonotopic vectors that link A1 and AAF. These two differences, in combination, have inspired a variety of new naming conventions and field demarcations for the mouse ACtx. The principal motivation for this study was to perform mesoscale optical imaging of GECIs in the mouse ACtx and develop objective, data-driven approaches to parcel the various fields. Widefield GCaMP6s imaging through chronically implanted cranial windows in awake mice confirmed the basic spatial layout of A1, AAF, A2, DP and IAF. We also observed the existence of high-frequency regions lateral to A1 and AAF as well as a region at the center of the ACtx that was weakly activated by pure tones. A closer examination revealed that this central region was tone-responsive, albeit with higher thresholds and lower response amplitudes. A pixel-based thresholding approach confirmed that best frequencies in this region formed a single tonotopic reversal between A1 and AAF. With this analytic adjustment in place, it was evident that tonotopic gradients within A1 and AAF did not bifurcate into two parallel lateral and medial fields, but instead formed a continuous tonotopically organized field. We developed an objective analysis approach to establish boundaries between fields based on points of tonotopic reversal or abrupt drops in signal amplitude. This analysis approach reveals strong tonotopic organization in A1 and AAF that “fans” out from low-frequency regions and collides at a single medial-lateral boundary, consistent with other species. Repeated imaging in the same mouse suggested that organization was reliable, with only minimal day-to-day variations, at least at this relatively coarse spatial scale.

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**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

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**Title:** Acoustical enrichment during early postnatal period improves responses of AI cortical neurons in adult rats

**Authors: *J. M. SYKA**, K. PYSANENKO, J. LINDOVSKÝ, Z. BUREŠ
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**Abstract:** It is well known that auditory experience during early development shapes response properties of auditory cortex (AC) neurons, affecting, e.g., tonotopical arrangement, response thresholds and strength, or frequency selectivity. Here we show that rearing rat pups in a complex acoustically enriched environment (AEE) leads to an improved representation of sounds in the AC when recorded later in adulthood, influencing spectral and temporal characteristics and also the reliability of neuronal responses. The acoustic enrichment comprised a continuous wide-band amplitude-modulated rippled noise with varying periodic spectral envelope complemented with several types of randomly occurring acoustic target signals, one of which triggered a reward release. The AEE was presented at 55 dB SPL (target stimuli at 60 dB SPL) 12 hours a day between postnatal days 14 and 28. Consistently with the results of our previous experiments on inferior colliculus (Bureš Z. et al., Acoustical enrichment during early postnatal development changes response properties of inferior colliculus neurons in rats. Eur. J. Neurosci. 40, pp. 3674–3683, 2014), the application of the AEE resulted in lower excitatory thresholds and better frequency selectivity of AC neurons. These changes were nonspecific and present at the whole range of neuronal characteristic frequencies. Importantly, the acoustic enrichment resulted in increased reliability of neuronal representation of the stimulus based both on the rate and the temporal codes. For a repetitive stimulus, the neurons in the AEE-exposed rats exhibited a lower spike count variance, indicating a more stable rate coding. The reduced variance was present both during the strong onset reaction and during the sustained part of the neuronal response. Also at the level of timing of individual spikes, the discharge patterns showed a higher degree of similarity across stimulus repetitions: the computed van Rossum distances of different spike trains evoked by the same stimulus were significantly smaller in the enriched animals. Furthermore, the neurons followed more precisely the temporal course of the stimulus, as manifested by better phase-locking (higher vector strength values) to frequency- and ampliude-modulated sounds. The results document that besides basic alterations of the receptive fields, the acoustic environment during the critical period of postnatal development permanently affects also the stochasticity, reproducibility, and fine structure of neuronal spiking patterns.

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**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

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**Topic:** D.06. Audition

**Title:** Temporal sound processing in the auditory cortex is influenced by changes in myelin integrity

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**Abstract:** The textbook view of myelin as a passive insulator has changed with the increasing understanding of the roles that oligodendrocytes (OLs) play in information processing in the brain. Even tough myelin plays a crucial role in action potential propagation, OLs have been shown to have important metabolic support roles, which might be essential during periods of high frequency firing. Since the auditory system is optimized for a fast and accurate timing along different stations, we aim to dissect to which extent myelin and OLs help maintain reliable firing in this sensory system. Specifically, we aim to understand how different degrees of dysmyelination affect auditory cortex responses to diverse physical sound properties. We recorded multiunit activity in the auditory cortex of anesthetized mice, using sounds protocols to test spectral and temporal processing. To test temporal acuity, we used a gap-in-noise detection protocol. This was paralleled by comparable behavioral tests, in order to understand the relationship between the neuronal responses and perception. Temporal reliability was tested through the continuous presentation of clicks at different stimulation rates. We used three mouse models with either **1)** complete (shiverer$^{-/-}$), **2)** partial (MPB-hypomorph$^{-/-}$), or **3)** cortical-specific (Emx1-cre::MBP$^{fl/fl}$) dysmyelination. As expected, we found that dysmyelination caused a major increase in response latencies, whose magnitude was correlated with the extent of dysmyelination. In addition, complete dysmyelination caused hyperexcitable responses, possibly due to the mislocalization of nodal channels. Complete dysmyelination also caused temporal acuity deficits, reflected in the neurons' inability to detect short silent gaps in a noise, and reliability deficits, observed in fatigue when responding to click sequences. Neither can be explained simply by a delay in conduction velocity. Strikingly, spectral processing appeared normal. Likewise, partial dysmyelination caused a reduction of behavioral temporal acuity, in the absence of a frequency discrimination deficit. In summary, we found that complete dysmyelination generated deficits only in auditory temporal processing. Partial dysmyelination generated similar effects at the behavioral level. This suggests that specifically temporal-detection mechanisms require axons that are not only fast and reliable, but also metabolically stable. These characteristics might be given by the structure of myelin and probably the OLs metabolic capacities, respectively.

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**Poster**

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**Topic:** D.06. Audition

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NIH R01 DC012984

**Title:** Distinct sensory and extra-sensory processing differences in two types of deep layer auditory cortex projection neuron

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**Abstract:** Neurons in layers (L) 5 and 6 of the auditory cortex (ACtx) give rise to a massive subcortical projection that innervates all levels of the central auditory pathway as well as non-auditory areas including the amygdala and striatum. L5 and L6 neurons feature distinct morphology, connection patterns, intrinsic membrane and synaptic properties, yet little is known about how these differences relate to sensory selectivity *in vivo*. Here, we performed cell-type-specific single-unit recordings and wide-field calcium imaging from two classes of ACtx L5 and L6 projection neurons; L5 corticocollicular neurons (L5CC), and L6 corticothalamic neurons (L6CT).
We first used an antidromic optogenetic “phototagging” approach to isolate individual L5CC and L6CT units on high-density multichannel probes in awake, head-fixed mice. We constructed a bank of complex stimuli by endowing noise tokens with randomly chosen acoustic parameters, and then quantified each neuron’s lifetime sparseness. We found that L5CC neurons had a lower lifetime sparseness index, indicative of reduced stimulus selectivity and a broader response distribution than L6CT neurons. Linear spectrotemporal receptive field fits were also able to explain a higher percentage of response variance in L6CT neurons, indicating a higher degree of linearity in their responses when compared to L5CC neurons. Recent studies have shown that an animal’s “internal state”, as indexed through locomotion or pupil diameter, exerts a powerful influence over ACtx excitability. We expressed GCaMP6s in L5CC and L6CT neurons and noted that bouts of locomotion were associated with opposite effects on the wide-field calcium signal: a decrease in L5CC neurons but a surprising increase in L6CT neurons. Collectively, these studies show that each class of deep-layer projection neuron performs distinct operations on internal and external signals, which likely impart distinct effects on their subcortical targets.

**Disclosures: R.S. Williamson:** None. **D.B. Polley:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

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**Topic:** D.06. Audition

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Cooperative Research Program of Primate Research Institute, Kyoto University

**Title:** Musical chord change detection in the macaque monkey is hindered by insertion of silent gaps between chords: a scalp ERP study

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**Abstract:** All animal and human auditory communications are limited in capacity by the listener's auditory functionalities for processing spectrotemporal features of sounds. Poor discrimination in frequency or time, for example, compromises the amount of receivable information per unit time. It is thus prudent to consider the possibility that the evolution of human auditory communication, hallmarked by language and music, was supported by some enhancement in auditory functions for processing spectrotemporal features of sounds.
This hypothesis was addressed by investigating whether humans and macaque monkeys differ in their ability to detect spectral changes over time, an ability fundamental to auditory information processing. Scalp event-related potentials (ERPs) were recorded while subjects listened to five-chord sequences played with two distinct articulations: staccato or legato. Chords (600 ms duration) were presented without gaps in the legato condition, while, in the staccato condition, a silent gap (300 ms) was inserted after each chord (300 ms). The final chord of the chord sequence was either identical to or different from the preceding four chords, which were always simple repetitions of a randomly chosen major chord.
In humans, the chord change in the final position evoked distinct brain responses around N1-P2-N2 latency in both legato and staccato conditions, as expected. Also in the monkeys, the chord change in the legato condition modulated the ERP around the N1-P2-N2 latency. However, the macaque ERP did not show any specific responses to the chord change in the staccato condition, suggesting that the chord change was undetected in the monkey.
The result echoes previous findings that discrimination of upward vs. downward frequency change in macaque monkeys is hindered by inserting a short gap (e.g., 200 ms) immediately before the frequency transition. Such disability can be explained by postulating that monkeys can detect frequency changes only when they occur within a short time window. Stated the other way

around, the human brain has evolved to have an extended time window for representing spectral changes, a capacity that would be beneficial for processing complex sound features that characterize music and language.

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**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** D.06. Audition

**Support:** IBS-R015-D1

**Title:** Modulation of neural activity during locomotion in the mouse auditory midbrain

**Authors: Y. YANG**, J. YANG, *G. KIM
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**Abstract:** Behavioral states can powerfully modulate sensory processing. This is highlighted by the recent evidence that neural activity is altered during locomotion, as has been demonstrated in visual and auditory cortices. Locomotion related suppression of neural activity has also been observed in the auditory thalamus, suggesting subcortical auditory stations are also impacted by behavioral states. However, the extent of this subcortical modulation and its relationships with cortical modulation remain unclear.
We recorded spontaneous and sound evoked neural activity in the inferior colliculus (IC) of awake head-fixed mice. During recording sessions, mice were free to run on a disc-shaped treadmill. Sound-evoked responses were probed by playing out 5 different pure tones (4, 8, 16, 32, 64 kHz, 100 msec duration) at 70 dB sound pressure level. A unit's response strength (RS) was quantified as the mean firing rate during the initial 25 msec of tone presentation with the baseline firing rate preceding the tone subtracted.
We analyzed neural activity of 39 single units recorded from the inferior colliculus. When mice were not walking, mean spontaneous firing rates ranged 0.1 to 79 Hz with the mean of 21±4 Hz. In 28 of the 39 units (72%), spontaneous firing rate was significantly modulated during locomotion. The modulation of spontaneous activity was bidirectional in that the rate increased by 319±82% in 22 units during locomotion, while the rate decreased by 54±11% in 6 units.
To determine whether sound-evoked activity of the IC neurons is also modulated during locomotion, we compared RS that measures the tone-evoked firing rate relative to the spontaneous rate between the non-walking and walking periods. Of the 27 units that showed excitatory response at the onset of a tone stimulus, 22 units showed significant modulation in RS.

During locomotion, RS decreased by 190±99% from the initial positive value in most units (n=21). In one unit, RS increased by 171% (n=1). In addition to the reduction in RS to tone stimuli, the units tended to show excitatory response at fewer frequencies during locomotion, indicating that the suppression leads to a narrower tuning (1.8±0.3 vs 1.1±0.2 tone frequencies; n=27).
By recording the neural activity of IC neurons in awake behaving mice, our results demonstrate that both spontaneous and sound-evoked activity of midbrain auditory neurons can be modulated during locomotion. Our results suggest that auditory midbrain neurons integrate internal behavioral states with external sound stimuli.

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**Poster**

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**Program#/Poster#:** 488.13/BB1

**Topic:** D.06. Audition

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NIH RO1DC9607

NINDS U01NS090569

**Title:** Neural correlates of pitch encoding in the auditory cortex of awake mice

**Authors:** ***S. SYLVESTER**[1], N. A. FRANCIS[1], K. SHILLING-SCRIVO[2], P. O. KANOLD[1]
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**Abstract:** Discrimination between auditory objects in music and speech is due, in part, to an object's perceived pitch. Key spectral and temporal predictors of pitch are the frequency and periodicity of the auditory object's fundamental frequency. Despite being heavily examined in both human and animal models, the neural correlates underlying pitch perception are not fully known. Past research has pointed to low frequency areas of the primary auditory cortex (A1) as the location of pitch perception in primates. However, non-primary regions have also demonstrated pitch-selectivity in non-primate animal models. In addition to the ambiguity of pitch encoding regions across animal models, the functional characteristics of pitch-selective neurons have not been examined extensively at the single cell level. In this study, we used a combination of wide-field and two-photon (2P) calcium imaging to acquire coarse and single cell resolution of neuronal activity across the auditory cortex of unanesthetized transgenic mice that express GCaMP6s, a calcium sensor, throughout the brain. Since different areas of the auditory

cortex may be implicated in pitch perception, we initially monitored calcium transients across primary and non-primary areas of the auditory cortex using wide-field imaging, and used two-photon microscopy for careful dissection of low frequency areas. To identify areas that respond to stimuli that evoke the percept of pitch, and to distinguish between frequency and temporal properties of sound, we presented dynamic iterated rippled noise (IRN) and pure-tones. Across trials, we detect consistent activation of small populations of neurons positioned within low and high frequency regions of the auditory cortex. 2P population averages of fluorescent responses during stimulus presentation showed variation in the velocity (ramping) of responses at different frequencies with steeper ramping occurring at frequencies below 1600Hz. By using IRN and different calcium imaging techniques, we are able to record the activity of hundreds of neurons simultaneously at single cell resolution and are able to image primary and non-primary regions of the auditory cortex at the same time. Together, our preliminary results suggests organization of pitch-selectivity in both low and high frequency regions of the mouse auditory cortex and dynamic responses to IRN.

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**Poster**

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**Title:** The organ of Corti extracts and processes the envelope pattern of a tonal complex

**Authors: *A. L. NUTTALL**[1], G. W. S. BURWOOD[2], A. FRIDBERGER[3]
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**Abstract:** Speech, music and animal communication calls contain many different frequencies that change rapidly over time. Yet, studies have shown that a limited amount of information about the slowly varying envelope of the stimulus is sufficient for accurate speech recognition, at least in quiet conditions. Direct evidence for this comes from cochlear implant users, most of whom get very good speech recognition when only a few frequency bands of envelope

information are presented through the implanted electrodes. Frequency components corresponding to the envelope are not found in the sound-evoked vibrations of the basilar membrane, but they are clearly present in the discharges of the auditory nerve. How can the auditory nerve encode information absent from the basilar membrane, which provides the stimulus that drives the nerve?
Using experiments in guinea pigs, we demonstrate that envelope extraction is possible because mechanically sensitive ion channels introduce distortion. This distortion tracks the envelope, excites the auditory nerve, and ensures that information about the envelope is transmitted to the brain. The hearing organ can therefore be viewed as a non-linear real-time extractor of the magnitude of the Hilbert transform of the acoustic stimulus.

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A*STAR Singapore

**Title:** Differential encoding of auditory information by subgroups of neuronal spikes associated with coordinated neuronal ensembles

**Authors:** ***J. SEE**, C. ATENCIO, V. SOHAL, C. SCHREINER
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**Abstract:** There is mounting evidence suggesting that sensory stimuli are processed by interconnected populations of neurons. However, most studies of information processing in the primary auditory cortex (AI) involve either single-unit spectrotemporal receptive field (STRF) estimation or paired neuronal correlation analyses, and assume that AI neurons filter auditory information either as individual entities or as pairs. Determining how AI encodes information will require an integrated approach that combines receptive field and multi-neuronal ensemble analyses.
To assess multi-neuronal information processing in AI, we performed dense extracellular recordings in rat AI while presenting dynamic, broadband stimuli. We used dimensionality reduction techniques to identify distinct groups of AI neurons (coordinated neuronal ensembles, or cNEs) that have reliable synchronous activity. We identified cNE events and used them to

assess spectrotemporal information processing. Neuronal spikes associated with cNE activity conveyed greater information than spikes that were not associated with cNE activity. For neurons that participated in multiple cNEs, spikes associated with one cNE had receptive field properties that were significantly different from that of spikes associated with other cNEs.
These findings challenge the classical idea that AI neurons produce a homogeneous set of spikes that may be equally weighted to estimate a single STRF. Instead, AI neurons can have multiple receptive fields based on associations with different cNEs, with each cNE representing the convergence of thalamocortical, intracortical and top-down inputs into AI. For each AI neuron, equally weighting all neuronal spikes to form a single STRF ignores this enhanced coding capacity. Therefore, by taking into account the stimulus preferences associated with each cNE, we may gain a more complete evaluation of information processing in AI.

**Disclosures: J. See:** None. **C. Atencio:** None. **V. Sohal:** None. **C. Schreiner:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 488.16/BB4

**Topic:** D.06. Audition

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NIH/NIDCD T32 DC000038 (ATL)

**Title:** Activation and deactivation of somatostatin-expressing GABA neurons disrupts temporal coding of sound frequency in the auditory cortex

**Authors:** *A. T. LANDAU[1], ***A. T. LANDAU**[1], *A. T. LANDAU[2], W. GUO[3], D. B. POLLEY[4,2]
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**Abstract:** The dynamic interplay between excitation and inhibition sculpts the neural representation of sound features at every stage of central auditory processing. At the level of the auditory cortex, where all inhibition is local, fast-spiking GABA cells balance the tuning of excitatory cells, but other populations of cortical GABA cells may play a crucial role in shaping cortical responses to sound. Here, we use an optogenetic strategy to manipulate and record from dendrite-targeting somatostatin-expressing (SST) GABA neurons in the primary auditory cortex (A1) of awake, head-fixed mice. We made extracellular recordings of single units from all layers of A1 using linear, multi-channel probes. A transgenic strategy was used to express

channelrhodopsin 2 selectively in SST interneurons. Sounds were presented when SST neurons were either activated via laser or immediately following laser offset (i.e., deactivation). We characterized the effects of SST neuron activation and deactivation on regular- and fast-spiking A1 units through a linear classifier that allowed us to determine how reliably sound frequency was encoded over time. Optogenetic activation of SST neurons bi-directionally modulated cortical excitability, strongly suppressing activity during laser stimulation but producing rebound excitation upon deactivation. Neurons typically exhibited a short-latency, prolonged response to their best frequency (BF); however, spectrotemporal encoding of preferred stimuli was disrupted during both activation and deactivation of SST neurons. Deactivation of SST neurons unmasked subthreshold input that destabilized frequency tuning preference over time. Together, these changes degraded cortical decoding of sound frequency, particularly when the stimulus decoder was trained with longer integration windows. Finally, a sliding window decoder revealed that frequency processing during modulation of SST neurons diverges from normal such that the decoder fell to chance just 25 milliseconds after tone onset. These results suggest that cortical SST neurons are necessary to shape the temporal dynamics of cortical encoding of sound. SST neurons synapse onto dendrites and control both dendritic integration and active dendritic mechanisms. Disrupting their activity may occlude their ability to shape the intraneuronal processing required to generate a robust, time-insensitive representation of elementary sound properties.

**Disclosures:** **A.T. Landau:** None. **W. Guo:** None. **D.B. Polley:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 488.17/BB5

**Topic:** D.06. Audition

**Support:** NIH F32 DC015966

**Title:** Transforming continuous temporal cues to a categorical spatial code in human speech cortex

**Authors: *N. P. FOX**[1], M. J. SJERPS[2], M. K. LEONARD[3], E. F. CHANG[4]
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**Abstract:** During speech perception, listeners extract acoustic cues from a continuous sensory signal to map it onto behaviorally relevant phonetic categories. Many such cues are encoded within the fine temporal structure of speech. For example, voice-onset time (VOT), the interval between a stop consonant’s release and the onset of voicing, distinguishes voiced (e.g., /b/, short

VOT) from voiceless (e.g., /p/, long VOT) stops in English. Despite the ubiquity of time-dependent cues like VOT in the world's languages, the neurophysiological mechanisms that allow listeners to distinguish sounds that differ along temporal dimensions remain unclear. To investigate this question, we recorded neural activity directly from the cortex of nine human subjects while they listened to and categorized syllables along a VOT continuum from /ba/ (0ms VOT) to /pa/ (50ms VOT). We found that spatially distinct neural populations respond preferentially to one category (either /b/ or /p/). In both populations, responses are sensitive to VOT differences within the preferred, but not the non-preferred, category. This graded VOT encoding rapidly evolves to reflect the ultimate (categorical) behavioral response function, showing that categorical perception of VOT emerges across time in auditory cortex. Additionally, /b/-selective responses are lagged depending on VOT, while /p/-selective responses are time-locked to the burst, suggesting differential sensitivity to spectral cues indicative of burst vs. voicing. To probe what computations might give rise to these response properties, we implemented a neural network model that simulates neuronal populations as leaky integrators tuned to detect either coincident or temporally-lagged burst and voicing cues. The same temporal dynamics and encoding patterns observed in real neural data emerged in the computational model, suggesting that local tuning for distinct spectral cues at precise lags may underlie temporal cue integration in auditory cortex. Finally, we also recorded neural responses to naturally-produced sentences containing multiple speech sounds differing in VOT (e.g., /d/ vs. /t/, /g/ vs. /k/). Results demonstrated that neuronal tuning for this temporal cue generalized across speech sounds containing different spectral cues. Our results provide direct evidence that continuous temporal information is transformed into a categorical spatial code by discrete, phonetically-tuned neural populations in human auditory cortex.

**Disclosures:** **N.P. Fox:** None. **M.J. Sjerps:** None. **M.K. Leonard:** None. **E.F. Chang:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 488.18/BB6

**Topic:** D.06. Audition

**Title:** Unique roles for delta and theta frequency bands in the cortical analysis of temporal speech structure

**Authors: *J. C. LEE**, A. J. FALCONI, T. OVERATH
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**Abstract:** Speech perception entails the mapping of the acoustic waveform to its linguistic representation. For this mapping to succeed, the speech signal needs to be tracked across a large temporal range at high temporal precision in order to decode linguistic units (phonemes,

syllables, words). Here we test how cortical processing of such temporal speech structure is modulated by higher-order linguistic analysis. To control the temporal scale of analysis, we used a novel sound-quilting algorithm that controls acoustic structure at different temporal scales (Overath et al., 2015). To control the linguistic content, we constructed speech quilts from both familiar and foreign languages. This ensures that any changes at the signal-acoustics level affect both languages identically, while manipulating the linguistic percept differently. Thus, neural responses that vary as a function of segment length, but are shared or similar across the two languages, suggest analysis at the signal-acoustics level, whereas neural responses that differ based on language familiarity imply the presence of linguistic processing. We recorded EEG while subjects listened to 6 s long English or Korean speech, quilted with 30 ms or 960 ms segment lengths. Neural entrainment to the speech quilt envelope, assessed via inter-trial correlation (ITC), in the theta band increased with segment length in both languages; however, ITC in the delta band increased with segment length only in English. This dissociation indicates that neural entrainment in the theta and delta frequency bands serves different functions: acoustic and linguist analysis of temporal speech structure, respectively. In particular, linguistic analysis tracks syllabic and word content that is preserved with increasing segment lengths. The results advance our understanding of the neural mechanisms underlying the acousto-linguistic mapping of temporal speech structure.

**Disclosures:** **J.C. Lee:** None. **A.J. Falconi:** None. **T. Overath:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 488.19/BB7

**Topic:** D.06. Audition

**Title:** Impact of articulator velocity-controlled rhythm in perceiving speech

**Authors:** ***S. HIROYA**[1], N. LAVAN[2], S. H. CHEN[3], S. MEEKINGS[4], S. K. SCOTT[5]
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**Abstract:** Speech sound is composed of temporal and frequency information. In perceiving speech, the role of frequency (segmental) information has been widely examined, but few studies have investigated that of temporal (supra-segmental) information. In linguistics, languages can be categorized into three different rhythms: stress-timed rhythm (e.g., English and German), syllable-timed rhythm (e.g., French and Spanish) and mora-timed rhythm (e.g., Japanese). It is known that acquisition of the foreign language is strongly affected by the learner's native language. For instance, native Japanese speakers tend to speak English to fit into mora-timed

rhythm of Japanese: The rhythm of English spoken by native Japanese speakers is less natural. We have proposed a method that can convert the speech rhythm of an English sentence spoken by a native Japanese speaker into stress-timed rhythm by a native English speaker. We have performed fMRI scans for native English speakers during passive listening and found that supplementary motor area (SMA) was more activated by Japanese (less natural) rhythm more than by English (natural) rhythm. This indicates that SMA involves in processing of language-dependent naturalness of rhythm. By the way, movements of articulators such as the lips and tongue, which reflect bell-shaped velocity profiles, generate speech. However, few studies have investigated the role of SMA in perceiving speech with non-biological velocity profiles. In this study, we developed a method that can convert temporal patterns of speech based on articulator velocity. The velocity was calculated from articulatory data, which were collected using the electromagnetic articulography (EMA) system. Forty English sentences were used. The bell-shaped velocity profile of natural speech was converted to emphasized, uniform and reversed velocity profile, without altering sentence duration. Sixteen native British English speakers participated in the experiment. They were asked to listen to the stimuli and repeat them. The result of speech intelligibility (percent keywords correct) showed natural = emphasized > uniform > reversed. Also, they were asked to rate the naturalness of speech rhythm. Results showed natural > emphasized > uniform > reversed. These indicate that speech intelligibility is affected by the non-biological articulator velocity profile, such as uniform and reversed, but naturalness of speech rhythm is affected by any manipulation of velocity profiles. By multivariate pattern analysis of fMRI data using these stimuli, we will be able to investigate the involvement of SMA related to the speech intelligibility and the naturalness of speech rhythm.

**Disclosures:** **S. Hiroya:** None. **N. Lavan:** None. **S.H. Chen:** None. **S. Meekings:** None. **S.K. Scott:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** D.06. Audition

**Support:** NIH F31 DC014903

NIH R01 DC014656

**Title:** Encoding of irregular amplitude modulations in gerbil auditory cortex

**Authors: *K. PENIKIS**, M. N. SEMPLE, D. H. SANES
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**Abstract:** The encoding of sound envelope by the auditory system is typically studied with periodic amplitude modulated (AM) stimuli. However, the relatively slow modulations found in the sound envelopes of species-specific vocalizations, including speech, are irregular. If neural responses to AM depend only on moment-to-moment changes in amplitude, then responses to periodic stimuli should predict the response to individual AM periods of corresponding duration when they occur within an irregularly fluctuating stimulus. We tested this assumption by measuring the responses of auditory cortex (ACx) neurons to stimuli with envelopes that were modulated with or without a fixed periodicity. The periodic stimulus was 4 Hz AM noise and irregular stimuli contained a range of periods between 1 and 16 Hz, centered at 4 Hz. Preliminary results indicate that, for most ACx units, the response to a standard 250 ms period (i.e., 4 Hz) presented in the middle of each trial was similar, regardless of whether the AM stimulus was periodic or irregular. This observation implies that ACx neurons may not depend on periodicity for encoding envelope. To explore this idea, we designed a second stimulus in which a continuous, dynamic stream of noise transitioned between periodic (AM rates of 2 to 64 Hz) and irregular (periods of 2 to 64 Hz interleaved randomly) sequences. With this stimulus, we can compare the full AM rate tuning functions constructed from periodic and from irregular trials. Taken together, these studies address the relationship between periodicity coding and the representation of the irregular envelopes found in natural stimuli.

**Disclosures: K. Penikis:** None. **M.N. Semple:** None. **D.H. Sanes:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

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**Title:** Developmental hearing loss impairs fast temporal processing

**Authors: *J. YAO**[1], D. SANES[2]
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**Abstract:** Fluctuations in sound level support speech comprehension, and perceptions of rhythm, prosody, and pitch, depending on the rate of amplitude modulation (AM). However, AM sensitivity may be vulnerable to hearing loss (HL) during its prolonged period of maturation. In fact, the processing of rapid (>100 Hz) modulation rates may be particularly impaired (e.g., Park

et al., 2015). Here, we sought to determine whether behavioral and neural AM detection thresholds display a similar sensitivity to developmental HL. Normal hearing (NH) adult gerbils, and those reared with conductive HL, were trained and tested on an appetitive Go-Nogo AM detection task (Go stimuli were broadband noise modulated at 64-512 Hz across a range of depths; Nogo stimulus was unmodulated noise). HL animals displayed poorer behavioral thresholds than NH animals at all AM rates, but performance was much worse at very fast rates, 256 and 512 Hz. To determine whether these perceptual deficits were attributable to degraded encoding mechanisms within the auditory brainstem, we recorded envelope following responses (EFRs) across a range of AM rates and depths from NH and HL animals that had been trained previously on the AM detection task. NH animals displayed similar EFR and behavioral thresholds, whereas HL animals displayed EFR thresholds that were better than those obtained behaviorally. This suggests that a neural deficit associated with behavioral impairment may be found downstream of the auditory brainstem. To test this idea, we are recording extracellular responses from ACx neurons while gerbils perform the AM detection task.

**Disclosures:** **J. Yao:** None. **D. Sanes:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

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**Program#/Poster#:** 488.22/BB10

**Topic:** D.06. Audition

**Support:** NIH Grant R01DC003180

**Title:** The representation of spatial location and temporal modulation in marmoset parabelt auditory cortex

**Authors: *D. GAMBLE**[1], X. WANG[2]
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**Abstract:** The current working model of primate auditory cortex comprises the hierarchical arrangement of a series of functionally distinct information processing stages: a primary 'core' region, a secondary 'belt' region, and a tertiary 'parabelt' region. The ‘auditory dual stream hypothesis’ suggests that caudal belt and parabelt regions form a ‘where’ pathway that selectively processes auditory location, whereas the rostral cortical fields form a ‘what’ pathway responsible for auditory identification. (Rauschecker 1997, Kaas & Hackett 2000, Romanski et al. 1999) Crucially, data testing this hypothesis have come only from studies in core and belt auditory cortex, and not parabelt. We analyzed single unit receptive field data from extracellular physiology studies in rostral and caudal parabelt in the the awake, behaving marmoset.

Unexpectedly, single units throughout parabelt, in both rostral and caudal regions, exhibited sharp tuning for spatial location similar to that found in earlier levels. Neurons in both fields also represented stimulus frequency and temporal modulation with sharp tuning and high fidelity. Thus both identity and location are represented faithfully in both auditory cortical pathways.

**Disclosures: D. Gamble:** None. **X. Wang:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

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**Topic:** D.06. Audition

**Support:** NIH grant R01 DC005216

Brain Imaging Initiative of the College Liberal Arts, University of Minnesota

**Title:** Cortical representations of attention to pitch or timbre

**Authors: *E. J. ALLEN**[1], P. C. BURTON[2], C. A. OLMAN[2], A. J. OXENHAM[2]
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**Abstract:** Pitch and timbre are two primary dimensions of auditory perception that are generally considered to be independent. However, under some circumstances they have been shown to interact with one another. For example, an increase in the fundamental frequency of a sound, the nearest physical correlate of pitch, can be confused for an increase in spectral centroid, a physical correlate of brightness (i.e., an attribute of timbre), and vice versa. An earlier passive fMRI study indicated that pitch and brightness are processed in largely overlapping regions of the auditory cortex, but their patterns of activation are separable via multi-voxel pattern analysis (MVPA). The aim of the current fMRI study was to determine whether allocating attention to one dimension or the other would make their cortical representations more spatially distinct. We collected BOLD data at 3T while participants listened to pairs of tones varying in either pitch, timbre, or both, and judged which tone had higher pitch or brighter timbre. While task performance was high in all conditions, subjects were significantly worse at performing the task when both dimensions were varying, confirming previous behavioral findings. Consistent with our previous results, we found that pitch and timbre engaged a common set of auditory regions with no clear distinctions at a univariate level. Furthermore, we found that increased attentional demands in the conditions in which both sound dimensions varied led to increased engagement of frontal regions, including the inferior and middle frontal gyri, compared to conditions in which just one dimension varied. However, heightened attentional demands did not appear to

improve the separability of the neural representations of pitch and timbre at either univariate, or multivariate levels. These results suggest that the computations underlying pitch and timbre perception are subserved by overlapping populations, likely on a scale that is difficult to disentangle without higher resolution and/or more sophisticated computational encoding models.

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**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

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**Topic:** D.06. Audition

**Support:** ERC

ISF- israel science foundation

**Title:** Cortical mechanisms underlying responses to temporal gaps

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**Abstract:** High temporal acuity of auditory processing is crucial for speech understanding. A Gap-detection test is used clinically to measure auditory temporal acuity. Abnormal gap detection thresholds are believed to reflect central hearing difficulties even in the presence of normal hearing sensitivity. In spite of their clinical relevance, cortical mechanisms for gap processing are poorly understood.
Using an oddball paradigm, we studied the coding of gaps in the rat auditory cortex. Gaps are composed of two noise markers separated by the gap duration. The sensory response to a gap consists of two components (called here P1 and P2), representing the responses evoked by the two markers. In cortex, these are usually mostly tonic responses. Because of forward masking, the P2 response is smaller than the P1 response, so that the P2/P1 ratio is typically smaller than 1.
We recorded responses to sequences consisting of either gap stimuli or continuous noise stimuli, and manipulated the probability of gap stimuli in the sequences. When the gap stimuli were rare (gap deviants), the P2/P1 ratio was greater than when the gap stimuli were common (gap standards). Moreover, in many neurons, when the gap was long (20ms), the P2/P1 was greater than 1, reversing the ubiquitous effect of forward masking. Thus, neurons in rat auditory cortex show strong Stimulus Specific Adaptation (SSA) to gaps, even at detection threshold (~ gap duration of 2ms).

Using intracellular recordings, we observed that in the P2 the excitation-inhibition (E/I) balance of the sensory response changes, with excitation becoming more prominent, accounting for the larger response of P2 when the gap is deviant. We hypothesize the existence of a class of neurons that are activated only by the second marker of the gap, and who are responsible on the large P2 excitatory response; such responses may arise from the action of disinhibitory circuits that are known to be present in cortex.

**Disclosures: B.H. Awwad:** None. **I. Nelken:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

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**Program#/Poster#:** 488.25/BB13

**Topic:** D.06. Audition

**Support:** NIH Grant DC-03180

**Title:** Missing fundamental pitch perception with semitone precision in marmosets

**Authors: *X. SONG**[1], M. S. OSMANSKI[2], X. WANG[3]
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**Abstract:** The perception of the missing fundamental, in which one perceives the fundamental frequency (F0) of a harmonic complex tone even when the F0 is removed, is one of the most important properties of pitch perception in humans. Some non-human species have also been shown to be sensitive to the pitch of missing fundamental sounds, although these previous animal studies have not demonstrated that this sensitivity to pitch has a precision comparable to that of humans. For humans to perceive Western musical melodies, a precision of at least one semitone is necessary. Marmosets (*Callithrix jacchus*), a highly vocal New World monkey species, have been shown to be able to discriminate a pitch difference of one semitone for harmonic complex tones with a periodicity of 440Hz (the standard A or A4 in ISO16). We hypothesized that marmosets also possess missing fundamental pitch perception with one semitone precision for the periodicity at 440Hz (A4). In the current study, marmosets were trained to discriminate harmonic complex sounds that differed in both periodicity (F0) and the presence of an F0 component. The animals exhibited a high hit rate when a probe sound differed from a reference sound only in periodicity. In contrast, the animal's hit rate was indistinguishable from the false alarm rate when a probe sound differed from the reference sound only in its F0 presence. These results show that marmosets discriminated these harmonic complex sounds based on their periodicity but not the presence of an F0 component, which suggest that they can

perceive the missing fundamental pitch. For a periodicity of 440Hz (A4), marmosets could perform this task even when the pitch change was as small as one semitone. Whereas for a periodicity of 220Hz (A3), the pitch change had to be increased to two semitones. Such an increase is also consistent with their perceptual sensitivity to temporal envelope cue changes on A3, but not A4. This difference in sensitivity suggests that the mechanisms for missing fundamental pitch perception change between A3 and A4. Together, our findings demonstrate that marmosets have the capacity to process missing fundamental pitch similar to humans with a precision of at least one semitone for the periodicity above A4. This is the first time that a non-human species has been shown to have the ability to discriminate the missing fundamental pitch at this precision, which suggests that marmosets may potentially be able to discriminate musical melodies.

**Disclosures:** **X. Song:** None. **M.S. Osmanski:** None. **X. Wang:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

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**Topic:** D.06. Audition

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Human Frontier Science Program

Biotechnology and Biological Science Research Council

**Title:** Excitatory ON and OFF receptive field arrangement confers direction selectivity to slow frequency modulation in mouse auditory cortex

**Authors: *G. A. CHAPUIS**[1], J. SOLLINI[2], C. CLOPATH[1], P. CHADDERTON[1]
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**Abstract:** Frequency-modulation (FM) is an important feature in human and animal communication. In the auditory cortex, the relative tuning of excitatory and inhibitory synaptic input accounts for direction selectivity at high modulation rates[1]. However, the mechanisms underlying direction selectivity at lower modulation rates relevant to vocalisation encoding have

not been established. We used multi-electrode arrays to record the activity of mouse auditory cortex neurons to pure tones and ascending and descending logarithmic FM sweeps (range: 2.2 - 140 octave/sec). Single units in the auditory cortex of fentanyl-anaesthetised animals exhibited the strongest directional selectivity at low modulation rates (< 8 octaves/second). Surprisingly, we found that the relative tuning of excitatory ON and OFF responses to pure tones was an excellent predictor of the units' direction selectivity (correlation coefficient $r = 0.61$, $p < 0.01$, $n = 30$ cells with V-shaped tuning curves to onset and offset). These results suggest that cortically generated synaptic inhibition may not be required for direction selectivity at low modulation rates. To test this proposal, we have selectively expressed the inhibitory DREADD in parvalbumin-positive (PV+) interneurons to manipulate fast spiking interneurons within the auditory cortex (AAV1/2-hSyn-DIO-hM4Gi-mCherry injected into the auditory cortex of PV-Cre mice; n = 6). Following IP injection of the agonist, clozapine-N-oxide, we demonstrate a strong increase in local field potential response to sound, consistent with a local reduction in cortical inhibition. We are currently analysing the directional selectivity of single units and measuring behavioural discrimination to ascending and descending sweeps in mice trained to perform a Go/No-Go task under conditions of reduced excitability of fast spiking interneurons. These experiments will establish the relative roles of ON and OFF-mediated synaptic excitation and cortical inhibition in the representation of slow modulations in sound frequency.

1)
Topography and synaptic shaping of direction selectivity in primary auditory cortex [doi:10.1038/nature01796]

**Disclosures:** **G.A. Chapuis:** None. **J. Sollini:** None. **C. Clopath:** None. **P. Chadderton:** None.

**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

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**Topic:** D.06. Audition

**Support:** NIH EB018783

W911NF-14-1-0440

**Title:** Passive mapping of receptive language function under general anesthesia

**Authors: *A. NOURMOHAMMADI**[1,2], A. DE PESTERS[1,2], P. BRUNNER[1,3], J. KNUTH[4], A. RITACCIO[3], G. SCHALK[1,2,5]
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**Abstract:** Resection of pathology is often necessary in patients with intractable epilepsy or brain tumors. Minimizing functional deficits resulting from that resection requires mapping of eloquent cortex, i.e., cortical locations involved in language, motor, or memory functions. Different methods have been developed for functional mapping including electrocortical stimulation (ECS), which is currently considered the gold standard. However, its application requires active participation of patients, and thus cannot be applied in patients who are not woken up from general anesthesia during surgery. Recent studies demonstrated that passive recordings of electrocorticographic (ECoG) activity can be used to rapidly produce functional maps of receptive language function that are concordant to those acquired using ECS mapping, but did also require active participation of the patient. In our study, we hypothesized that it is possible to derive such functional maps in people under general anesthesia.
In our study, we presented auditory speech stimuli to eighteen patients under anesthesia. Our analyses demonstrated that these speech stimuli did not result in detectable ECoG changes during deep stages of anesthesia. At the same time, during induction of, or emergence from anesthesia, they did elicit ECoG broadband gamma responses in localized cortical regions typically associated with receptive language function. Additional analysis in the subset of patients who underwent chronic implantation of ECoG grids—patients with intractable epilepsy who were awake for periods of several days—demonstrated that the locations identified for receptive language function during anesthesia were usually on or close to the locations identified during the awake state.
The preliminary results demonstrated the possibility of mapping of receptive language function during general anesthesia. With further verification and additional protocol optimizations, our protocol could greatly expand the range of patients that can benefit from mapping of receptive function.
**Keywords:** functional brain mapping, electrocorticography, awake craniotomy
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**Poster**

**488. Auditory Processing: Temporal, Frequency, and Spectral Processing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 488.28/BB16

**Topic:** D.06. Audition

**Support:** The Whitehall Foundation

NARSAD Young Investigator Award

Startup Funding from George Washington University

**Title:** Diverse configuration of synaptic tonal receptive fields in the auditory midbrain

**Authors: J. LEE**, J. LIN, *G. K. WU
The George Washington Univ., Washington, DC

**Abstract:** The inferior colliculus (IC) is a major integrative hub of auditory processing, as multiple ascending projections from lower auditory nuclei converge towards the central nucleus of the IC. The interactions of converging excitation and inhibition produce a variety of response properties that either modulate or create new responses. Recently, imbalanced excitation and inhibition has been observed among a subset of neurons in the IC and the primary auditory cortex. However, the detailed structure function of these neurons' excitatory and inhibitory receptive fields were still obscure, especially their relationship with characteristic frequency and complex sound such as frequency-modulated (FM) sweeps. Here we applied in vivo whole cell voltage-clamp recordings to the central nucleus of the IC of mice and systematically examined the receptive field properties of neurons within a single isofrequency laminae. In contrast to the systematic change of the imbalance between excitatory and inhibitory receptive fields along the tonotopic axis in the auditory cortex and the IC of rats, diverse configurations of balance of synaptic receptive fields have been observed with similar characteristic frequency. Moreover, these neurons with the same characteristic frequency but different balance of excitation and inhibition demonstrated selectivity to FM sweeps. It suggests that mouse IC neurons could selectively respond to much narrower range of FM, which could be a neural substrate for their responses to more complex sounds, such as vocal signals.

**Disclosures: J. Lee:** None. **J. Lin:** None. **G.K. Wu:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.01/BB17

**Topic:** D.06. Audition

**Support:** NSERC of Canada

**Title:** Reduced acoustic startle response and peripheral hearing loss in the 5xFAD mouse model of Alzheimer's disease

**Authors: *R. E. BROWN**[1,2], T. P. O'LEARY[4], J. WANG[3]
[1]Psychology & Neurosci., Dept. of Psychology and Neurosci., Halifax, NS, Canada; [3]Sch. of Human Communication Disorders, [2]Dalhousie Univ., Halifax, NS, Canada; [4]Univ. of British Columbia, Vancouver, BC, Canada

**Abstract:** Hearing dysfunction has been associated with Alzheimer's disease in humans, but there is little data on the auditory function of mouse models of Alzheimer's disease. Furthermore, characterization of hearing ability in mouse models is needed to ensure that tests of cognition that use auditory stimuli are not confounded by hearing dysfunction. Therefore we assessed acoustic startle response and pre-pulse inhibition in the double transgenic 5xFAD mouse model of Alzheimer's disease from 3-4 to 16 months of age. The 5xFAD mice demonstrated an age-related decline in acoustic startle as early as 3-4 months of age. We subsequently tested Auditory Brainstem Response (ABR) thresholds at 4 and 13-14 months of age using tone-bursts at frequencies of 2- 32 kHz. The 5xFAD mice showed increased ABR thresholds for tone-bursts between 8 and 32Khz at 13-14 months of age. Finally, cochleae were extracted and basilar membranes were dissected to count hair cell loss across the cochlea. The 5xFAD mice showed significantly greater loss of both inner and outer hair cells at the apical and basal ends of the basilar membrane than wildtype mice at 15-16 months of age. These results indicate that the 5xFAD mouse model of Alzheimer's disease shows age-related decreases in acoustic startle responses, which are at least partially due to age-related peripheral hearing loss. Therefore, we caution against the use of cognitive tests that rely on audition in 5xFAD mice over 3- 4 months of age, without first confirming that performance is not confounded by hearing dysfunction.

**Disclosures: R.E. Brown:** None. **T.P. O'Leary:** None. **J. Wang:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.02/BB18

**Topic:** D.06. Audition

**Support:** NIH Grant 3T32NS041218-15S1

NIH Grant 5R01MH099505-05

NIH Grant 3R01NS097762-01S1

**Title:** Pharmacological inhibition of substantia nigra pars reticulata and sensorimotor gating function: Implications for differential organization of nigral outflow between rodents and monkeys

**Authors: *B. L. AGUILAR**[1,2], L. MALKOVA[2], P. A. FORCELLI[2]
[2]Dept Pharmacol & Physiol and the Interdisciplinary Program in Neurosci., [1]Georgetown Univ., Washington, DC

**Abstract:** Sensorimotor gating is a fundamental process through which the central nervous system filters motor responses to stimuli; this process can be assessed operationally through measurement of prepulse inhibition (PPI) of the acoustic startle response (ASR). ASR is attenuated by presentation of a low-intensity prepulse prior to the startle-inducing stimulus; this phenomenon is well-conserved across species.
Previous studies in rodents have reported (Koch et al., 2000) that lesions of substantia nigra pars reticulata (SNpr) impair PPI. Prior work from our group has shown that the macaque SNpr displays a discrete behavioral topography that is not seen in rodents (Dybdal et al.). Here, we sought to directly compare the effects of reversible pharmacological inhibition of the SNpr across these species.
For the rodent studies, 12 Long Evans rats were surgically implanted with bilateral cannulae inserted into the SNpr. After recovery, either muscimol (2nmol) or saline was intracerebrally microinfused into the SNpr. Rats were tested following either unilateral or bilateral drug administration. We found that muscimol infusion significantly impaired PPI in rats ($P<0.05$, Repeated measures ANOVA). These data are consistent with the prior lesion studies.
For the non-human primate studies, 5 rhesus macaques were surgically implanted with a microinfusion platform. After recovery, a structural MRI scan was run to determine infusion coordinates in the SNpr. Prior to PPI testing, muscimol (9nmol) was intracerebrally microinfused unilaterally. Contrary to our findings in the rat, muscimol infusion into the macaque SNpr **potentiated** prepulse inhibition.
Studies are currently underway examining the role of specific nigral output targets using optogenetic silencing in rats. We propose that a differing architecture of nigral outflow mediates this species difference.

**Disclosures: B.L. Aguilar:** None. **L. Malkova:** None. **P.A. Forcelli:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.03/BB19

**Topic:** D.06. Audition

**Title:** Stochastic resonance as a putative cause of tinnitus

**Authors: *P. KRAUSS**, K. TZIRIDIS, C. METZNER, A. SCHILLING, U. HOPPE, H. SCHULZE
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**Abstract:** Subjective tinnitus is generally assumed to be a consequence of hearing loss. In animal studies it has been demonstrated that acoustic trauma induced cochlear damage can lead to behavioral signs of tinnitus. In addition it was shown that noise trauma may lead to

deafferentation of cochlear inner hair cells even in the absence of elevated hearing thresholds, and it seems conceivable that such hidden hearing loss may be sufficient to cause tinnitus. Numerous studies have indicated that tinnitus is correlated with pathologically increased spontaneous firing rates and hyperactivity of neurons along the auditory pathway. It has been proposed that this hyperactivity is the consequence of a mechanism aiming to compensate for reduced input to the auditory system by increasing central neuronal gain, a mechanism referred to as homeostatic plasticity (HP), thereby maintaining mean firing rates over longer timescales for stabilization of neuronal processing. Here we propose an alternative, new interpretation of tinnitus-related development of neuronal hyperactivity in terms of information theory. In particular, we suggest that stochastic resonance (SR) plays a key role in both short- and long-term plasticity within the auditory system and that SR is the primary cause of neuronal hyperactivity and tinnitus. We argue that following hearing loss, SR serves to lift signals above the increased neuronal thresholds, thereby partly compensating for the hearing loss. In our model, the increased amount of internal noise - which is crucial for SR to work - corresponds to neuronal hyperactivity which subsequently causes neuronal plasticity along the auditory pathway and finally may lead to the development of a phantom percept, i.e. subjective tinnitus. We demonstrate the plausibility of our hypothesis using a computational model and provide exemplary findings in human patients that are consistent with that model. Finally we discuss the observed asymmetry in human tinnitus pitch distribution as a consequence of asymmetry of the distribution of auditory nerve type I fibers along the cochlea in the context of our model.

**Disclosures:** **P. Krauss:** None. **K. Tziridis:** None. **C. Metzner:** None. **A. Schilling:** None. **U. Hoppe:** None. **H. Schulze:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.04/BB20

**Topic:** D.06. Audition

**Support:** NIDCD / NIH

**Title:** Psychophysics of auditory streaming based on spectral and spatial cues in rhesus monkeys

**Authors:** ***J. LEE**[1], T. BANNO[1], Y. I. FISHMAN[2], Y. E. COHEN[1,3,4]
[1]Otorhinolaryngology - Head and Neck Surgery, Univ. of Pennsylvania, Perelman Sch. of Med., Philadelphia, PA; [2]Neurol., Albert Einstein Col. of Med., Bronx, NY; [3]Neurosci., [4]Bioengineering, Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** A fundamental aspect of hearing is parsing auditory stimuli into discrete perceptual representations of sounds in the environment. The auditory system accomplishes this parsing, in

part, by grouping acoustic stimuli with similar spatial or and spectral features into one perceptual stream and separating those with different features into different streams. However, the degree to which spectral and spatial cues contribute to sound-stream segregation has not been fully elucidated, especially in non-human primates.
Here, we tested how the degree to which spectral and spatial cues affected the ability of rhesus monkeys to effectively group or segregate acoustic stimuli into separate auditory sound streams by conducting a series of psychophysical experiments. Specifically, we presented two sequences of alternating interleaved tone bursts that varied in frequency, sound level, and spatial separation from a free-field speaker array. Monkeys were trained to report hearing a deviantly loud tone burst. This report served as a proxy for stream segregation: by design, this deviant could only be detected if the two sequences of tone bursts were perceived as separate streams[1,2].
As expected, we found that monkeys' ability to detect the deviant tone greatly improved as the frequency difference between the two tone-burst sequences increased. Likewise, as the spatial separation between the two sequences increased, the ability to detect the deviant tone was also substantially enhanced. Interestingly, spatial separation, in this paradigm, was a more potent segregation cue than spectral separation.Interestingly, spatial cues, in this paradigm, served aswere a more potent segregation cue than spectral cues. Furthermore, spatial and spectral cues interacted synergistically to facilitate deviant detection and hence stream segregation. Psychophysical findings are consistent with human performance on a comparable task. This study provides the first demonstration of the combined effect of spectral and spatial cues on auditory streaming in non-human primates.

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1. Sussman, E. & Steinschneider, M. "Attention effects on auditory scene analysis in children". *Neuropsychologia* **47**, 771-785 (2009).
2. Sussman, E. S. & Steinschneider, M. "Attention modifies sound level detection in young children". *Dev Cogn Neurosci* **1**, 351-360 (2011).

**Disclosures:** **J. Lee:** None. **T. Banno:** None. **Y.I. Fishman:** None. **Y.E. Cohen:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.05/BB21

**Topic:** D.06. Audition

**Support:** JEPS KAKENHI Grant Number JP15H01671

**Title:** Neural processing of delayed auditory feedback of involuntary self-body movement

**Authors: *T. MOMOKAWA**[1], K. UENO[2], S. SHIMADA[1]
[1]Electronics and Bioinformatics, [2]Architecture, Meiji Univ., Kawasaki-shi, Kanagawa, Japan

**Abstract:** Predicting the timing and occurrence of auditory stimulus is an important feature of auditory processing. Our previous study showed that a delayed auditory feedback of self-action elicits the event-related potential (ERP) component named enhanced-P2 (EP2) (Toida et al., 2016). To further investigate the characteristics of the ERP component, we examined whether EP2 is also elicited by delayed auditory feedback of the involuntary self-body movement as that of the voluntary movement. Fifteen healthy students (7 female, 8 male; aged 21.7 ± 1.6 years) participated in the experiment. We employed an oddball paradigm with a non-delayed 1000-Hz pure tone as the standard stimulus and a delayed 1000-Hz pure tone as the deviant stimulus. Auditory stimulus was presented in association with mouse-click that was caused every 1-2 second involuntarily. In the experiment, the deviant stimulus was temporally delayed from their mouse-click. We introduced four delay conditions (100, 200, 300, and 400 ms) and the control condition (non-delayed). Participants were told to silently count the number of trials in which they could detect the delayed auditory stimulus. The EEG (g.USBamp, g.tec, Austria) signals were recorded at 30 channels of the 10% system with a digital 0.5-30 Hz band-pass hardware filter. The sampling frequency was 512 Hz. The region of interest (ROI) was determined as Pz in order to compare the results with that of our previous study (Toida et al., 2016). The EP2 was also observed in the current experiment. However, while it was observed only in the 100 and 200 ms delay conditions in the previous study (Toida et al., 2016), the current result showed that the EP2 was not observed in the 100 ms delay, appeared only in the 200 and 300 ms delay, and diminished in the 400 ms delay condition. We have argued that EP2 reflects a 200-300 ms temporal window for integrating self-body information (Toida et al., 2016). The present result suggests that the internal generation of the auditory feedback prediction in the involuntary movement is slower for about 100 ms than in the voluntary movement because efference copy is not available in the involuntary movement.

**Disclosures:** **T. Momokawa:** None. **K. Ueno:** None. **S. Shimada:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.06/BB22

**Topic:** D.06. Audition

**Title:** Auditory brainstem responses recorded from inferior colliculus in Miniopterus fuliginosus

**Authors: *T. FURUYAMA**[1], K. HASE[2], S. HIRYU[2], K. I. KOBAYASI[2]
[1]Doshisha Univ., Kyoto, Japan; [2]Grad. Sch. of Life and Med. Sci., Doshisha Univ., Kyotanabe, Japan

**Abstract:** The auditory brainstem responses (ABR) are consisted of short-latency waves that collectively contain the neural evoked potential. The ABR are used for comparative indicators of

hearing sensitivities. We measured the hearing sensitivity in *Miniopterus fuliginosus* for comparison with properties of acoustic signals and neuronal frequency tuning. The ABR was recorded from inferior colliculus of three awake bats. The 20 types of frequencies of tone pips between 4 and 94 kHz were presented to the subjects. We decreased systematically intensities of tone pips to obtain a threshold of ABR at different frequencies of tone pips. Auditory stimuli were presented for 100 times, and the ABR to each frequency were averaged at each intensity level. As results, the audiogram has a U-shape over the frequency range from 16 to 94 kHz. In addition, the most sensitive frequency region of 44-56 kHz occurs at the terminal portion of echolocation pulses that are down-sweeping sounds. Latencies of ABR were extended along decreasing intensities of stimuli by 7.5 to 11.2 μs/dB at frequency range between 44-56 kHz. These results will be compared with other species of bats.

**Disclosures: T. Furuyama:** None. **K. Hase:** None. **S. Hiryu:** None. **K.I. Kobayasi:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.07/BB23

**Topic:** D.06. Audition

**Support:** NIH Grant R01EY025978

Veterans Administration

Emory University Undergraduate Research Program

**Title:** Listening to the mind's iPod: Are there two kinds of auditory imagery?

**Authors: L. RAJAN**[1], *S. A. LACEY[1], K. SATHIAN[1,2]
[1]Emory Univ., Atlanta, GA; [2]R&D Ctr. for Visual and Neurocognitive Rehabil., Atlanta VAMC, GA

**Abstract:** Individual differences in both visual and haptic imagery can be organized along a continuum of preferences for object and spatial imagery subtypes. Object imagers tend to integrate surface properties, such as color and texture, with structural information about shape. By contrast, spatial imagers tend to ignore surface properties and instead focus on structural information and spatial transformations. Here, we tested whether there are corresponding subtypes of auditory imagery and whether musical expertise is a factor. Participants (n=28: m 10, f 18; musicians = 15, non-musicians = 13) listened through earphones to 12-tone sequences in which each tone (of constant pitch and duration) varied in loudness and whether it was played in the right or left channel. The task was to discriminate the spatial pattern (a structural property) across changes in the loudness pattern (a surface property) and vice versa. Poor discrimination of

the spatial pattern across loudness changes would indicate integration of structural and surface properties and reflect the auditory equivalent of object imagery. Poor discrimination of the loudness pattern across changes in the spatial pattern would indicate that surface properties were not attended and reflect the auditory equivalent of spatial imagery. Participants' imagery preferences were classified by their scores on the Object-Spatial Imagery and Verbal Questionnaire, a measure of visual imagery preferences (object imagers = 20, spatial imagers = 8). Participants also completed the Montreal Battery of Evaluation of Amusia (MBEA: Peretz et al., 2003, Ann NY Acad Sci 999:58-75). Consistent with our visual and haptic studies (Lacey et al., 2011, Exp Brain Res 213:267-273), we found that differences in auditory performance tracked participants' visual imagery preference: object imagers could not discriminate the structural property over a change in the surface property while spatial imagers could not discriminate the surface property if the structural property changed. There were no significant differences between musicians and non-musicians and no interactions with musicianship status, nor were MBEA scores correlated with performance. There were no gender differences or interactions. We conclude that there are two kinds of auditory imagery corresponding to object and spatial subtypes, and that the propensity to integrate surface properties into an image (object imagery) or to favor structural properties (spatial imagery) is a multisensory organizing principle of mental imagery across the three modalities of vision, haptics, and audition.

**Disclosures: L. Rajan:** None. **S.A. Lacey:** None. **K. Sathian:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.08/BB24

**Topic:** D.06. Audition

**Support:** "973" program of China 2014CB943002

NSFC of China U1301225

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**Title:** Hippocampal reactivity relaying from medial septum only to noise in awake forebodes the sensibility of auditory fear conditioning independent of the sound characteristics

**Authors: *C. XIAO**, Y. LIU, Z. XIAO
Dept. of Physiol., Southern Med. Univ., Guangzhou, China

**Abstract:** Hippocampus integrates various sensory information including visual, tactile, olfactory and auditory, and plays a critical role in many higher-order brain functions especially for learning and memory. It is thought to receive projection from auditory cortex indirectly and process sound information, such as the conditioning stimulus in auditory fear conditioning. However, it is systematically unexplored whether or not the neurons in hippocampus can respond to sound and distribute tonotopically. Using in vivo loose patch recording we found that neurons in hippocampus (CA3, CA1 and entorhinal cortex) respond to noise stimuli only in awake and almost not to pure tone (2-64 kHz) unlike in auditory cortex. What intriguing was that the response latencies (13 ms) of neurons in hippocampus responding to noise stimuli were much shorter than those (18 ms) in auditory cortex. It hints that the auditory pathway of hippocampus may be from other nuclei rather than auditory cortex. Hippocampus receives a strong projection from medial septum. Thus we explored the neuronal responses to noise and pure tone in medial septum. The response characteristic was same as that in hippocampus, but the shortest response latencies (10ms) to noise were shorter than those in hippocampus. Furthermore, silenced the medial septum with lidocaine or muscimol the neuronal discharges in CA3, CA1 and entorhinal cortex decreased significantly even disappeared. Whereas silenced auditory cortex, the responses almost unchanged. It is interpreted that the auditory pathway of hippocampus uploads from medial septum rather than auditory cortex. Hippocampus is involved in auditory fear conditioning and sensitive only to noise, so we hoped that silencing medial septum with lidocaine or muscimol during training would abolish auditory fear conditioning with noise as conditioning stimulus rather than pure tone. Interestingly, not only was the noise induced fear behavior blocked but also 2.5 kHz induced fear behavior when silenced medial septum. It seems that auditory fear conditioning behavior is independent of the characteristics of sound. Then, we trained mice with noise, 2.5, 5, 10, 15, or 30 kHz as conditioning stimulus respectively, and tested the conditioned behavior with noise, 2.5, 5, 10, 15, and 30 kHz after 24h. The freezing behaviors were not significantly different. Our findings suggest that the hippocampus relaying from medial septum responses only to noise stimuli in awake, and that the excitability of hippocampal neurons to noise forebodes the sensibility of auditory fear conditioning, which is independent of the characteristics of conditioning sound.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.09/BB25

**Topic:** D.06. Audition

**Support:** NIDCD 5R01DC009224

**Title:** Spiking activity in auditory cortex to identity-preserving changes in sounds

**Authors: *F. A. RODRIGUEZ CAMPOS**[1], J. MCDERMOTT[2], Y. E. COHEN[3]
[1]Univ. of Pennsylvania, Antiguo Cuscatlan, El Salvador; [2]Brain and Cognitive Sci., MIT, Cambridge, MA; [3]Dept. Otorhinolaryngology-Head Neck Surgery, Univ. of Pennsylvania Dept. of Otorhinolaryngology, Philadelphia, PA

**Abstract:** The auditory system transforms acoustic stimuli into representations that subserve perception, recognition, and behavior. One major challenge faced by the auditory system is the creation of sound representations that are invariant to identity-preserving transformations. Indeed, sound recognition by human listeners is invariant to changes in the stimulus due to variation in the pitch of speakers' voices, the location of the sound source, the amount of background noise, etc. The brain areas, neural mechanisms and computations that provide the basis for a listener's tolerance to identity preserving changes are unknown.To address the neural basis of invariant recognition, we conducted large-scale recordings from the auditory cortex of rhesus monkeys while they listened to natural sound exemplars (animal vocalizations and natural background noises) and identity-preserving transformations of these exemplars. These transformations included sound-source location and room reverberation. Additionally, as controls, we presented scrambled versions of these sounds. These scrambled versions were statistically matched to these natural exemplars but could not be identified as originating from the same source as the original sounds. We recorded with MicroProbes' 96-electrode Microwire Brush Array simultaneously from 3 areas of auditory cortex: anterolateral belt (AL), middle-lateral belt (ML), and primary auditory cortex (A1). We report how identity-preserving transformations of sounds are represented in the spiking activity of neurons in these three brain regions. In particular, we describe the degree to which neural populations codes support perceptual representations of invariance.

**Disclosures: F.A. Rodriguez Campos:** None. **J. McDermott:** None. **Y.E. Cohen:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.10/BB26

**Topic:** D.06. Audition

**Support:** RES/0164/7500/158

**Title:** Primate behavioral and functional-imaging model for auditory figure-ground segregation

**Authors: *F. SCHNEIDER**, P. DHEERENDRA, F. BALEZEAU, A. THIELE, T. D. GRIFFITHS
Inst. of Neurosci., Newcastle Univ., Newcastle Upon Tyne, United Kingdom

**Abstract:** Segregating sounds in a noisy environment is a fundamental aspect of scene analysis. Inability to detect figures from noisy background is a ubiquitous problem in both cochlear hearing loss and in disorders of central sound processing. In normal human listeners, emerging evidence suggests that auditory objects are detected with remarkable sensitivity and robustness based on a mechanism that detects temporal coherence in different frequency bands (Teki et al. 2013). Human imaging studies demonstrate a system including auditory cortex in the superior temporal sulcus (STS) in non-core homologues and in the intraparietal sulcus (IPS) during preattentive, stimulus-driven figure-ground decomposition of stimuli (Teki et al. 2016; Teki et al. 2011). We have developed a primate model in a species in which the system organisation can be compared to humans more easily than in other mammals (Baumann et al. 2013). The eventual aim is to achieve an understanding of figure-ground analysis at the neuronal level based on systematic recordings that are not possible in humans. We present data from behavioural experiments to measure the ability of rhesus macaques (n = 3) to detect target sounds in a noisy background using stimuli and parameters determined by the previous human work (Teki et al. 2013). A Go/No-Go task with bar release measured the detection of figures based on keeping 10 frequencies constant in a random chord sequence where each chord had duration of 50ms. Parallel functional imaging using fMRI on 3 subjects demonstrated the network for detection of similar 10-component figures presented over 40 chords with a duration of 50ms. As in previous human fMRI (Teki et al. 2011) an irrelevant task was carried out with the aim of demonstrating preattentive, stimulus-driven figure-ground detection. Sparse imaging was used. A contrast between scans after presentation of figure plus ground and control trials after figure only demonstrated activity in parabelt homologues in anterior superior temporal gyrus (STG). In one subject we demonstrated significant activity in posterior STS.

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Teki, S. et al. (2016): Neural correlates of auditory figure-ground segregation based on temporal coherence. Cereb Cortex 26:9
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Teki, S. et al. (2011): Brain Basis for Auditory Stimulus-Driven Figure-Ground Segregation. J Neurosci 31(1):164-171

**Disclosures: P. Dheerendra:** None. **F. Balezeau:** None. **A. Thiele:** None. **T.D. Griffiths:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.11/BB27

**Topic:** D.06. Audition

**Title:** Evaluation of acoustic information related to discriminability in avian higher-order auditory cortex

**Authors: *M. INDA**, R. TABATA, K. HOTTA, K. OKA
Keio-Univ. Biophysics and Neuroinformatics Lab., Yokohama/Kanagawa, Japan

**Abstract:** Some animals use specific sounds as a communication tool, and they discriminates these sound by extracting precise acoustic information in noisy natural environment. Zebra Finch (*Taeniopygia guttata*) also uses their songs as the communication tool between males and females. Male songs consist of motifs that have stereotyped sequences of syllable with various acoustic information (e.g. Fundamental Frequency, FM, AM, etc.), and females choose their mating partners by distinguishing songs of males. In avian brain, caudal medial mesopallium (CMM) is known as a higher-order auditory region that has a function of sound discriminability. According to previous research, CMM neurons indicated discriminable activities between conspecific and heterospecific songs, but not between unfamiliar and familiar song (Woolley and Doupe, 2008). These studies are, however, based on results from difference in neural responses to different sound stimuli. It is only evaluated whether it can discriminate or not, thus little is known about what the essential information for sound discriminability..In this study, we clarify this problem by designing synthetic stimulus for focusing on acoustic information of male songs. To investigate detailed mechanism of sound discriminability, we obtained neural activities from CMM neurons when we presented conspecific songs and several synthetic stimulus sounds to anesthetized female zebra finches. To quantify sound discriminability of these neural activities, we calculated receiver operating characteristic (ROC) values from the firing rate. We found that there is a tendency that sound discriminability depends on syllable types. Furthermore, to investigate differences of acoustic information between discriminable and indiscriminable syllables, we estimated relationship between ROC values and some acoustic parameters of syllables by making acoustic information surface. From these analysis, we could observe sound discriminability changes depending on combination of particular 2 acoustic information. Then, we found a boundary between discriminable and indiscriminable syllables on Mean Frequency and Entropy acoustic information surface. Furthermore, we set ROC values as the 3rd on this surface to evaluate more detail of relationship between discriminability and these 2 acoustic information. When we saw this 3D space from particular direction, we found a positive correlation. These results suggested that the factor of song discriminability depends on relationship between Mean Frequency and Entropy.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.12/CC1

**Topic:** D.06. Audition

**Support:** ISF 51/11 (I-CORE cognitive sciences)

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FP7 CIG

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ISF 762/16

European Society of Anaesthesiology

**Title:** Breakdown of intercortical signaling upon propofol anesthesia: An intracranial human study of auditory responses using single-unit, LFP, iEEG and ECoG data

**Authors: *A. J. KROM**[1,6], A. MARMELSHTEIN[2], H. GELBARD-SAGIV[3], A. TANKUS[7,4], D. HAYAT[8], I. STRAUSS[9], M. SOEHLE[10], J. BOSTRÖM[11], F. MORMANN[12], I. FRIED[13,9], Y. NIR[5]
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**Abstract:** **Background**:
It is still unclear how, despite diverse molecular and cellular mechanisms, a wide range of anesthetics all bring about loss of consciousness (LOC) and how responses to sensory stimuli differ between wakefulness and anesthesia. Specifically, it remains undecided whether “just hypnotic” anesthesia primarily disrupts feedforward activity up to primary sensory regions via “thalamic gating” or alternatively whether it mainly affects intercortical signaling.
**Methods**:

We recorded ECoG, intracerebral EEG (iEEG), microwire LFPs, and neuronal spiking activity across multiple brain regions of seven epilepsy patients as they were sedated for routine deplantation of intracranial depth/ECoG electrodes serving for clinical monitoring.
Propofol infusion rate was increased gradually over 20-40 minutes (5 to 400 mcg/kg/min) while auditory stimuli (40Hz click-trains, dynamic random chords and words) were presented during wakefulness, deepening sedation, and after achieving unresponsiveness. Patients were instructed to respond to a target word stimulus via a push-button.

**Results**:

During wakefulness, significant iEEG responses to 40Hz click-trains (n=328 depth electrodes) were observed across widespread cortical areas, whereas during anesthesia responses were strongly attenuated and restricted to regions around auditory cortex. This attenuation occurred suddenly around LOC.
In the auditory cortex (Heschel's Gyrus and Superior Temporal Gyrus), the effects of anesthesia on 40Hz responses were more moderate and variable. In response to words during wakefulness, auditory LFPs showed an increase in broadband high-frequency gamma (40-110Hz) power and concurrent decrease in alpha/beta (10-20Hz) power ('desynchronization'). During anesthesia, gamma effects (likely reflecting feedforward processing) were largely preserved, whereas alpha/beta effects (likely reflecting top-down processing) were strongly attenuated.
Preliminary results from spiking responses of auditory neurons showed complex and variable effects of anesthesia on auditory response properties. We are currently investigating to what extent this variability can be explained by factors such as the precise auditory field, early vs. late response components, and stimulus complexity.

**Conclusion**:

Anesthesia preferentially disrupts intercortical aspects of auditory responses such as the spread of activity from A1 to high-order cortical nodes and top-down response signatures, while relatively sparing early bottom-up signaling up to A1.
*AJK & AM contributed equally

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.13/CC2

**Topic:** D.06. Audition

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**Title:** Neural correlates of sine wave speech intelligibility in human frontal and temporal cortex

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**Abstract:** Auditory speech comprehension is the result of neural computations that occur in a broad network that includes the temporal lobe auditory cortex and the left inferior frontal cortex. It remains unclear how representations in this network differentially contribute to speech comprehension. Here, we recorded high-density direct cortical activity during a sine wave speech (SWS) listening task to examine detailed neural speech representations when the exact same acoustic input is comprehended versus not comprehended. Listeners heard SWS sentences (pre-exposure), followed by clear versions of the same sentences, which revealed the content of the sounds (exposure), and then the same SWS sentences again (post-exposure). Across all three task phases, high-gamma neural activity in the auditory cortex superior temporal gyrus was the same, distinguishing different words based on bottom-up acoustic features. In contrast, frontal regions were active only when the input was comprehended, which corresponded with stronger representational separability among spatiotemporal activity patterns evoked by different words. We observed this effect only in participants who were not able to comprehend the stimuli during the pre-exposure phase, indicating a direct relationship between frontal high-gamma activity and speech understanding. Together, these results demonstrate that both frontal and temporal cortical networks are involved in spoken language understanding, and that under certain listening conditions, frontal regions are involved in discriminating speech sounds.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

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**Topic:** D.06. Audition

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W911NF-14-1-0440

**Title:** Characteristics of phase resetting in low-frequency oscillatory activity during a reaction time task

**Authors: *L. MOHEIMANIAN**[1,2], W. COON[3], P. BRUNNER[1,4], G. SCHALK[1,2,4]
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**Abstract:** Understanding the mechanisms that underlie behavioral performance (e.g., reaction time) could lead to improvements in diagnosis and treatment for people affected by disorders of the central nervous system. Oscillatory brain activity affects perceptual and behavioral performance, and represents rhythmic changes in the excitability of neuronal populations in the cortex. Previous studies have suggested that oscillatory phase may be aligned to facilitate quick reaction to external stimuli. This sudden change in oscillatory phase (termed as phase reset) is associated with enhanced cortical excitability and improved behavioral performance. However, the relationship of phase reset with population level activity and its spatio-temporal dynamics have not been studied, making it difficult to infer whether this is a localized or widespread mechanism. In this study, we were interested in determining the spatio-temporal relationship between phase reset and population level activity (i.e., broadband gamma activation). Specifically, we investigated the temporal relationship between phase reset, stimulus onset and broadband gamma activation across wide cortical areas.
To accomplish this, we recorded electrocorticographic (ECoG) activity from frontal, parietal and temporal cortices in eight human subjects while they performed a reaction time task. In this task, subjects were asked to press a push button as quick as possible in response to a salient auditory stimulus. In our single-trial analysis, we determined the timing of phase reset from the band-pass filtered ECoG activity (3-8 Hz) and the timing of the broadband gamma power onset (70-170 Hz). Our results show that phase reset occurs approximately 45 ms after stimulus onset and prior to broadband gamma activation. Interestingly, the delay between phase reset and broadband gamma activation is constant in hand motor cortex, but not in other cortical areas. Finally, our results show that phase reset is a widespread cortical mechanism. These results contribute to a more comprehensive understanding of the neural basis of behavioral performance.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

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**Topic:** D.06. Audition

**Support:** NIH Grant R01 DC005779

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**Title:** Selective auditory attention to a single sound stream suppresses responses to temporally non-coherent sounds in ferret auditory cortex

**Authors: *K. LU**, W. LIU, J. B. FRITZ, S. A. SHIHAB
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**Abstract:** Human listeners can focus attention on speech of a single speaker in a noisy auditory scene. This ability requires segregating the relevant sound stream and ignoring irrelevant sound sources. Our previous studies proposed that temporal coherence plays an important role in segregating sounds. When ferrets were trained to globally attend to two tone-sequences without any behavioral requirement to differentiate or segregate them, we found that coherent activation of cortical neurons tuned to the two tones (when the sequences were synchronous) induced excitatory interactions (or binding) between them; by contrast, asynchronous tones induced incoherent activation and suppressive interactions the two different frequency channels. The current studies tested the effects of *selective* attention when ferrets were trained to focus attention on one of the sequences while ignoring the other sounds. We hypothesized that the attended channel would bind all channels that are coherent with it, while suppressing actively those incoherent with it. Two ferrets were trained to listen attentively to detect a small intensity change in a sequence of narrow bandpass noise bursts. This foreground target stream occurred against a background of sequences of two alternating tones: one tone sequence was synchronized with the target noise sounds, while the other tone sequence was out of phase with the target stream (temporally alternated with the target sequence). Using standard neurophysiological techniques, we recorded auditory responses of single units (N=84) in the primary auditory cortex (A1) of behaving animals. Responses from A1 neurons tuned to the tone streams that alternated with targets were significantly suppressed, while responses from neurons tuned to tones that were synchronized with the targets remain intact, providing further support for the temporal coherence hypothesis as the neural mechanism underlying the ability to filter out irrelevant sounds in complex auditory scenes.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

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**Title:** Sex differences in lifespan prolongation effect in mice induced by acoustic environmental enrichment

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**Abstract:** Environmental enrichment (EE) has been reported to have positive effects on experimental animals including prevention of frailty signs, and accelerations of developments and functions of the brain. A typical experimental setting of EE consists of the interaction of complex factors including larger cages with variety of objects enhancing animal's physical activity and larger groups of animals with the opportunity for more social interaction. In the current study, we simplified the experimental condition and focused on the effect of enrichment of acoustic sensory stimuli through the observations of lifespan and voluntary movements in mice.
Ninety-six 8-week old C57Bl/6J mice were assigned to three groups (16-male and 16-female per group and 4 animals per cage) with different acoustic environmental conditions throughout the experiment: (1) acoustically enriched environmental condition with full range (~100kHz) sounds (FRS condition), (2) acoustically enriched environmental condition with high-cut (~20kHz) sounds (HCS condition), and (3) standard environmental condition with only background noise (control: CNT condition). In FRS and HCS conditions, tropical rain forest sounds were presented through two speakers fixed at the top of each cage. Other properties of environment including cage size were standard rearing condition of experimental animals. Voluntary movements were continuously monitored with a computerized system throughout lifespan.
The mice of HCS condition showed significantly longer lifespan (nearly 17%) and significantly

increased voluntary movements than those of CNT condition. FRS condition also showed a similar tendency although the statistical significance did not reach the predetermined threshold. There was no significant correlation between the voluntary movements and lifespan, suggesting that the increase of voluntary movements was not a primary cause of prolongation of lifespan. In addition, there was sex difference in the effects of acoustic EE. Namely, the prolongation of lifespan was more prominent in male mice, and only in male, the minimal lifespan of each cage was significantly prolonged in FRS and HCS conditions than that of CNT condition. In addition, the variance of lifespan of mice within each cage was significantly smaller in FRS and HCS conditions than that of CNT condition, suggesting that the prolongation of lifespan induced by acoustic EE may result from the changes in the relationship of individuals, i.e. social dominance, which is predominantly observed in male mice.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

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**Topic:** D.06. Audition

**Support:** German Academic Exchange Service (DAAD)

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**Title:** Phase entrainment of neural oscillations is causally relevant for neural responses to intelligible speech

**Authors: *B. ZOEFEL**, A. ARCHER-BOYD, M. H. DAVIS
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**Abstract:** Alignment between neural oscillations and speech rhythm, “entrainment”, is often enhanced during speech comprehension. Nevertheless, the relation between entrainment and comprehension might merely be correlational, introduced by stimulus manipulations that simultaneously reduce speech intelligibility and remove entraining cues for neural oscillations. Only if we manipulate entrainment as a dependent variable and observe consequences for speech comprehension, can we can conclude that there is a causal relation between the two. This is possible using transcranial alternating current stimulation (tACS): tACS has been shown to impose a rhythm on neural oscillations and can thus be used to manipulate entrainment in an experimental setting. However, based on behavioural measures alone, it is difficult to distinguish a specific modulation of speech processing and changes to low-level auditory processes that

would affect processing of non-speech or unintelligible stimuli.
We therefore combined tACS at 3.125 Hz over lateral temporal regions with concurrent fMRI to measure BOLD responses to intelligible (16-channel vocoded) and unintelligible (1-channel vocoded) rhythmic speech stimuli. We manipulated entrainment by systematically varying the phase relation between tACS and speech rhythm, and measured the consequences for neural activity (reflected in the BOLD response) in speech-specific and auditory brain regions.
We found that, for intelligible speech, the relation between tACS phase and speech rhythm significantly modulates the magnitude of the BOLD response in the Superior Temporal Gyrus (compared to a surrogate distribution). Importantly, this modulation was specific to tACS stimulation during intelligible speech; a significant interaction showed that the effect was reduced and absent for unintelligible speech and during sham stimulation. Our results therefore suggest that entrainment has a specific, causal influence on neural responses to intelligible speech. We anticipate that tACS can have a specific effect on enhancing speech perception and comprehension which we will explore in follow-up behavioural studies.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

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The Hoover Fund

**Title:** Electrocorticographic (ECoG) investigation of auditory predictive coding in the human brain across levels of consciousness

**Authors: *K. V. NOURSKI**[1], M. I. BANKS[2], A. E. RHONE[1], M. STEINSCHNEIDER[3], H. KAWASAKI[1], M. A. HOWARD, III[1]
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**Abstract:** Predictive coding models of sensory processing emphasize the integration of feedforward and feedback information streams across the sensory cortical hierarchy. Studies employing local/global deviant (LGD) stimulus paradigms (e.g. Bekinschtein et al., 2009, PNAS 106: 1672-7) offer promise for elucidating the neural basis of sensory awareness. Non-invasive studies show that responses to local (within-trial) deviance are robust to changes in the level of consciousness, whereas responses to global (across-trial) deviance are not. Non-invasive recordings offer limited opportunity to investigate the contributions of specific cortical regions to these processes. This study used electrocorticography (ECoG) to refine the localization of LGD responses and test their sensitivity to loss of consciousness (LOC) under general anesthesia. Subjects were neurosurgical patients undergoing removal of intracranial electrodes placed to identify epileptic foci. Stimuli were four repetitions of a vowel, followed by the same or different 5th vowel (local deviant). Global deviance was manipulated by varying the percentage of "same" and "different" patterns. The stimuli were presented during an awake baseline period and during induction of general anesthesia with stepwise increases in propofol dose. The subjects were instructed to respond to global deviants with a button press. ECoG recordings were simultaneously made with depth electrodes implanted in the superior temporal plane and subdural grid electrodes implanted over the hemispheric convexity. Analysis of cortical activity focused on event-related potentials (ERPs) and high gamma (70-150 Hz) power. Local deviance effect - increased ERP amplitude and high gamma power - was localized to auditory cortex on the superior temporal plane and lateral superior temporal gyrus. Increases in high gamma power were more spatially restricted compared to ERP effects. Global deviance effect extended to auditory-related areas, had longer latencies and reflected the subjects' task performance. Induction of general anesthesia led to an early abolishment of global deviant effect, followed by abolishment of local deviant effect in non-primary auditory cortex. Local deviant effect in core auditory cortex was resistant to general anesthesia. Data demonstrate differential effects of general anesthesia on preattentive (local deviance) and higher-level predictive coding (global deviance) mechanisms of novelty detection in the human auditory cortex. LOC is associated with early suppression of higher-level predictive coding processes, followed by attenuation of preattentive components of auditory novelty detection.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

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Hoover Fund

**Title:** Effects of propofol anesthesia on connectivity within the human auditory cortical hierarchy: An intracranial electrophysiological study

**Authors: *M. I. BANKS**[1], K. V. NOURSKI[2], H. KAWASAKI[3], M. A. HOWARD, III[4]
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**Abstract:** While anesthetic action on subcortical sites likely contributes to loss of consciousness (LOC), there is an emerging consensus on the importance of disrupted cortical network connectivity, a model with extensive, but indirect, experimental support. Previously, we showed in murine core auditory cortex that feedback cortical pathways are differentially sensitive to suppression by general anesthetics compared to thalamocortical feedforward pathways. Whether this applies to the human cortical hierarchy is unclear. We addressed this issue using electrocorticographic (ECoG) recordings in neurosurgical patients during induction of propofol anesthesia.

Subjects were undergoing removal of intracranial electrodes placed to identify epileptic foci. ECoG recordings were made simultaneously with depth electrodes implanted in superior temporal plane and subdural grid electrodes implanted over the hemispheric convexity. We focused on analysis of resting-state data recorded in 5 minute blocks interleaved with responses to a local global deviant (LGD) paradigm .Data were collected during an awake baseline period and during induction of general anesthesia with incrementally titrated propofol infusion. We focused on nodes in the auditory cortical hierarchy that were responsive during the LGD paradigm: posteromedial and anterolateral Heschl's gyrus (PMHG, ALHG), planum temporale (PT), superior and middle temporal gyrus (STG, MTG), supramarginal gyrus (SMG), inferior and middle frontal gyrus (IFG, MFG). Spectral analysis was performed using multitaper methods. Functional connectivity (FC) was measured as weighted phase lag index (WPLI) in conventional frequency bands (delta to gamma), and changes in connectivity were related to with Euclidean distance between electrodes.

In SMG, IFG and MFG, propofol anesthesia was associated with large, wideband increases in spectral power, with the largest increases in the alpha band, but modest or no changes in spectral power elsewhere. Under waking conditions, gamma FC was high locally within auditory cortex (PMHG, ALHG, PT), but was lower elsewhere. Alpha FC was lower in magnitude but more far ranging. Gamma FC was largely resistant to anesthesia, whereas alpha FC, especially between distant nodes, was enhanced under anesthesia.

Data demonstrate frequency band- and region-specific effects of general anesthesia on network connectivity along the human auditory cortical hierarchy. Modest effects on gamma-band WPLI

are consistent with sparing of feedforward cortical connectivity. Enhanced connectivity in the alpha band may contribute to the loss of consciousness during induction of general anesthesia.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

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**Topic:** D.06. Audition

**Support:** Auditory Vestibular Research Enhancement Award Program

**Title:** EEG measurement of cognitive systems during effortful listening

**Authors: *D. RYAN**[1], S. SMITH[1], E. SELLERS[2], M. A. ECKERT[3], K. SCHAIRER[1]
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**Abstract:** Adults with hearing loss who report difficulty understanding speech with and without hearing aids often also report increased mental or listening effort. Although speech recognition measures are well known and have been in use for decades, measures of listening effort are relatively new and include objective measures such as working memory tasks, pupillometry, heart rate, skin conductance, and brain imaging. The purpose of this study is to evaluate an electroencephalogram (EEG)-based method to assess cognitive states associated with high-frequency alpha (10-13 Hz), low-frequency alpha (8-10 Hz), and theta (4-8 Hz) during effortful listening. Changes in high frequency alpha have been associated with semantic memory and cognitive demands. Low-frequency alpha has been associated with working memory. In addition, changes in theta have been associated with encoding information and increased listening effort. Correlations between EEG frequency recordings, self-report, and behavioral measures in speech recognition and auditory working memory tasks will be described. Results will be presented demonstrating the extent to which high frequency alpha predicts word recognition in noise performance and self-reported listening effort.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

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**Topic:** D.06. Audition

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Brain Science Project of the Center for Novel Science Initiatives (CNSI), National Institutes of Natural Sciences (NINS) (BS281005)

**Title:** An anesthetic dose of ketamine disrupts mismatch activity in common marmosets

**Authors: *M. KOMATSU**[1], N. ICHINOHE[1,2]
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**Abstract:** Mismatch negativity (MMN) is a component of event-related potentials evoked by violations of the regularity in sensory stimulus-sequences in human. MMN has been receiving attentions as a clinical and translatable biomarker of psychiatric disorders such as schizophrenia. In agreement with the glutamatergic hypothesis of schizophrenia, N-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine, elicit many symptoms of schizophrenia when administered to normal human subjects or macaque monkeys, including reductions in the MMN. In this study we sought to effects of NMDA-receptor blockade using anesthetic administration of ketamine on MMN in common marmosets. We recorded the electrocorticograms (ECoGs) from two common marmosets with epidurally implanted electrodes covering a wide range of cortical regions. The 28-32 channel ECoG array was epidurally implanted on the left hemisphere of each marmoset. ECoG recordings were conducted 15 min after ketamine administration (30 mg/Kg i.m.). We used a roving oddball paradigm, in which repetitive tone-sequences with 20 types of frequency (250-6727 Hz with an interval of 1/4 octaves) were randomly presented. We considered the last tones of sequences as standards, and the first tones of sequences as deviants. First, we calculated ERPs for standards and deviant stimulus, respectively. Then, difference wave is obtained by subtracting the deviant stimulus ERP from the standard stimulus ERP. In the case of awake marmosets, we have previously reported MMN-like activity in the temporal area and mismatch related activity in the frontal and parietal areas. In the case of ketamine anesthetized marmosets, we found temporal MMN disappeared or diminished and the frontal and parietal mismatch related activity disappeared. These results suggest that MMN in marmosets' temporal area is formed through the interactions with frontal and parietal areas, and ketamine disturbs the interactions.

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**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

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**Title:** Distinct timescales of population coding in auditory and parietal cortices

**Authors: *C. A. RUNYAN**[1], E. PIASINI[3], S. PANZERI[4], C. D. HARVEY[2]
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**Abstract:** The canonical organization of cortical circuits has led to the hypothesis that similar basic computations are performed across the cortex. However, the nature of information represented across the cortical hierarchy differs qualitatively, suggesting the possibility that the structure of population codes may differ across cortex. For example, auditory cortex (AC) represents sound stimuli that can fluctuate over tens of milliseconds, while in posterior parietal cortex (PPC), decision tasks can require the maintenance of information for several seconds. We hypothesized that population activity dynamics could differ between sensory and association cortex in order to represent information at different timescales. We imaged the activity of populations of ~50 neurons in AC and PPC, using the calcium indicator GCaMP6f, while mice performed a navigation-based sound localization task in a visual virtual reality environment. We developed a generalized linear model (GLM) to predict the activity of individual neurons using the measured behavioral variables. A Bayesian decoder based on the GLM predictions revealed sound stimulus information in AC but not PPC, and information about the mouse's choice in both regions. We characterized the functional "coupling" among neurons in AC and PPC by measuring the GLM prediction improvement when including activity of other simultaneously imaged neurons as additional predictors. The AC population was only weakly coupled: activity

of other neurons provided little prediction improvement. In contrast, the PPC population was highly coupled: activity of other neurons greatly improved the model's performance beyond what could be explained by task and behavioral features. The coupling in PPC extended across long time lags, including up to 1 second. Reasoning that time-lagged coupling could affect the timescale of the population code, we quantified the population coding timescale as the temporal consistency of the population decoder output. This timescale was twice as long in PPC as in AC. Disrupting coupling with trial shuffling shortened this timescale in PPC, but not AC. Finally, coupling and consistency were higher in PPC in trials in which the mouse performed the task correctly than in error trials. We conclude that AC and PPC populations operate in different modes. AC neurons respond independently of one another across time, resulting in a population code with a short timescale that can respond to moment-to-moment fluctuations in sensory stimuli. In contrast, responses of PPC neurons are highly interdependent across time, allowing for a population code with a long timescale that can accumulate and maintain information.

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**Poster**

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**Program#/Poster#:** 489.23/CC12

**Topic:** D.06. Audition

**Support:** NIH Grant RO1DC004263

**Title:** Parallel processing of attended and unattended pattern violations in complex listening environments

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**Abstract:** To successfully process the complex mixture that enters the ears, listeners must distinguish sounds of interest from unattended background sources. Attention can facilitate this processing by enhancing the representation of attended sounds in working memory; however, the degree of processing of unattended sounds is debated. Work in our laboratory, using pure tones, indicates that unattended sound streams are structured in working memory but there is a limitation on the processing of sound events within the streams. We hypothesized that increasing the distinctiveness of sound streams would strengthen automatic stream segregation and thereby decrease the overall processing load. We predicted that increasing the number of acoustic features that define each stream would allow for a greater degree of within-stream processing of unattended sounds. Event-related brain potentials (ERPs) were used as a covert measure of sound

processing. Normal-hearing adult participants performed a selective listening task in one condition and watched a movie while passively listening to the sounds in another condition. ERPs evoked by pattern violations in the unattended sound streams served as an index of within-stream processing. A similar pattern of ERP responses to unattended pattern violations were obtained between passive and active listening conditions. Our results show that in contrast to previous studies that used pure tones, when the distinctiveness of each auditory stream was high, it facilitated automatic stream segregation. Natural sound sources are defined by multiple acoustic features; thus these results indicate that non-selective processing occurs in parallel during selective listening in noisy environments.

**Disclosures: R.M. Symonds:** None. **E.S. Sussman:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.24/CC13

**Topic:** D.06. Audition

**Title:** Acoustic startle response for tinnitus screening: Concepts, statistics and limitations

**Authors: *A. SCHILLING**, P. KRAUSS, K. TZIRIDIS, H. SCHULZE
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**Abstract:** A standard behavioral paradigm for objectively measuring a possible tinnitus percept in rodents is the paradigm proposed by Turner and coworkers in 2006 based on prepulse inhibition (PPI) modulation of the acoustic startle response (ASR) measurements obtained before and after an acoustic trauma. The major advantage of this method compared to other behavioral paradigms for tinnitus screening in animals is the absence of pre-training and therefore the lack of induction of additional cortical plasticity. However, to date no good statistical method exists to clearly determine if an animal has developed a tinnitus precept or not. Many approaches are based on simple averaging of the obtained PPI values and population comparisons without the possibility to perform valid statistics on the level of the single animal.
We here present a new statistical approach to overcome these limitations. In a first step we show that startle response amplitudes are not normal distributed. We estimate the distribution of the calculated PPIs by the full combinatorial power of all measured amplitudes and show by qq-plotting that the PPI values are approximately lognormal distributed, allowing parametrical testing of the logarithmized values. For comparison of pre and post trauma PPI distributions it has to be taken into account that the obtained values by full combinatorial power are not independent anymore. We present a statistical approach coping with this problem and finally allowing valid statistical statements about changes of PPI and about possible tinnitus percepts in animals.

**Disclosures:** **A. Schilling:** None. **P. Krauss:** None. **K. Tziridis:** None. **H. Schulze:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.25/CC14

**Topic:** D.06. Audition

**Support:** Gravitation Grant 024.001/006 of the Language in Interaction consortium

**Title:** From behaviour to genes: Perceptual effects of FoxP1

**Authors:** ***F. HEIM**[1,2,3], K. RIEBEL[1], S. E. FISHER[2,4], C. SCHARFF[3], C. TEN CATE[1,5]
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**Abstract:** Forkhead box proteins (FoxPs) are implicated in vocal communication in humans. Different speech and language phenotypes have been associated with specific mutations in the respective genes encoding these transcription factors which are highly homologous across the animal kingdom. Interestingly, parallels have been discovered in phenotypes associated with dysfunctions of neuronally expressed FoxPs in different species. Experimentally manipulated versions of FoxPs, for instance, lead to altered vocalisations in vocal learning and non-learning animals.
In brains of juvenile and adult songbirds such as the zebra finch (*Taeniopygia guttata*), FoxPs are also found to be expressed. Expression of FoxPs has been observed not only in nuclei involved in song learning and production such as Area X, but also in brain regions associated with song perception that are present in female birds. However, only male zebra finches sing a song, which they learn from a tutor, whereas females do not sing. Thus, expression patterns of FoxPs across sexes and vocalisation types suggest broader roles for these transcription factors in other aspects of vocal communication, beyond their well-studied contributions to vocal production, such as auditory perception.
In order to test the role of FoxPs in adult female zebra finches, we induced a bilateral lentivirally-mediated FoxP1 knockdown in the song nucleus HVC, investigating local contributions of the gene to auditory perception. The knockdown animals were screened for behavioural differences during tasks that rely on auditory perception, using preference tests and Go/NoGo tests. Subsequently, the virally targeted brain areas were dissected and used for RNA sequencing, to investigate changes in transcriptional activity that might be linked to altered behavioural responses.
While knockdown individuals maintained their natural preference for their father's song, their internal motivation to listen to stimulus songs appeared greatly decreased as determined by lower

pecking activity to trigger playback. During tests for song preference, discrimination and categorization of altered stimuli, the knockdown and control birds performed equally well. RNA sequencing results supported the conclusion that FoxP1 plays a role in the intrinsic motivation to listen to a specific song without affecting a bird's ability to identify different sounds.
These preliminary results regarding the functions of FoxP1 in song perception and listening behaviour might shed light on the engagement of FoxPs in auditory feedback and perception which are, next to vocal motor control, critical processes underlying human speech and language learning.

**Disclosures: F. Heim:** None. **K. Riebel:** None. **S.E. Fisher:** None. **C. Scharff:** None. **C. ten Cate:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.26/CC15

**Topic:** D.06. Audition

**Support:** MK - AIHS Postdoctoral Fellowship

MK - NSERC CREATE in BIF postdoctoral fellowship

NA - NSERC CREATE in BIF doctoral fellowship

CIC - AIHS Summer Studentship

MHM - NSERC Discovery Grant #40352

MHM - Alberta Alzheimer Research Program

**Title:** Modulation of auditory cortex responses to pure tones by optogenetic stimulation of excitatory neurons in the posterior parietal cortex, using behavior and electrophysiology methods

**Authors: *M. KYWERIGA**, N. AFRASHTEH, C. I. CHADWICK, N. PATEL, J. STEIN, M. H. MOHAJERANI
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**Abstract:** The posterior parietal cortex (PPC) is a multi-modal sensory association area involved in auditory, visual and somatosensory perception. The auditory cortex (AC) and PPC have modest reciprocal connections and the PPC shows robust responses following sound presentation. We have replicated these findings in our own hands and hypothesized that the PPC serves in a modulatory role over the auditory cortex.
To test this hypothesis, we first performed pilot electrophysiology experiments in a small cohort

of wild-type mice to search for local field potential and multi-unit responses to pure tone pips in the PPC. We found a “hot-spot” of activity corresponding to previously reported location of PPC in layer V, which we then targeted for fiber optic implantation for further electrophysiological and behavioral characterization in transgenic mice. We used two cohorts of mice expressing Channelrhodopsin-2 in either excitatory neurons or parvalbumin (PV) interneurons using Thy1-ChR2 and PV-Ai32 strain mice respectively.
One month prior to electrophysiology experiments mice (N = 8) were implanted with a single ferrule over the left PPC. Under isoflurane anesthesia, we performed a craniotomy and durotomy over the left auditory cortex and inserted a multi-shank silicone probe into layer V. During tone presentation, we stimulated the PPC with 473 nm blue light that was continuously active for 320 ms, beginning 10 ms before sound onset until 10 ms after sound offset. We found that laser stimulation of excitatory PPC neurons caused a significant reduction of the peak LFP onset responses to pure tones. On the other hand, laser stimulation of inhibitory PPC neurons had no effect on the LFP onset responses.
We next trained water-deprived mice (N = 14), implanted with fiber optics over bilateral PPC, in the two-tone forced-choice operant conditioning paradigm. To initiate a trial the mouse poked its nose into a central port causing a single 300 ms tone to be played. To receive a small water reward, the mouse had to select the left port for low tones (8 - 11.3 kHz) or the right port for high tones (11.3 - 16 kHz). Once trained, we randomly delivered laser stimulation in half of the trials using the same parameters as above. We found that laser stimulation of excitatory PPC neurons caused strong behavioral deficits. However, laser stimulation of PPC PV interneurons had no effect on behavior.
These behavioral and electrophysiological results suggest that the PPC is responsible for suppression of onset responses to pure tones in the anesthetized mouse. Additionally, the PPC appears to be necessary for performance on the tone discrimination task.

**Disclosures:** **M. Kyweriga:** None. **N. Afrashteh:** None. **C.I. Chadwick:** None. **N. Patel:** None. **J. Stein:** None. **M.H. Mohajerani:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

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**Topic:** D.06. Audition

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Institute of Critical Technologies and Applied Sciences at Virginia Tech

**Title:** Sensorimotor integration in the biosonar system of horseshoe bats

**Authors: *J. SUTLIVE**[1], H. RIQUIMAROUX[3,4,5], R. MUELLER[2,3]
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**Abstract:** Bats have evolved unique methods of perception to navigate and catch prey using ultrasonic sounds. It has been observed that the greater horseshoe bat (*Rhinolophus ferrumequinum*) rapidly move their pinna and noseleaf structures in coordination with pulse emission and echo reception during echolocation, with everything occurring on a 100ms time scale. Sensorimotor integration is not uncommon in neural systems but bats provide a unique case for auditory processing coinciding motion in the periphery. We have developed biomimetic robotic models to replicate the dynamic emission and reception elements of bat echolocation; current data have shown these dynamics introduce time-variant effects which encode information to inform object identification and location. We have planned experiments to understand how motor and auditory systems are integrated, which will be done by recording midbrain responses interacting with stimuli. These recordings will consist of field potential measurements taken from the inferior and superior colliculi; we hope this work will provide physiological events associated with sensorimotor integration for echolocation.

**Disclosures: J. Sutlive:** None. **H. Riquimaroux:** None. **R. Mueller:** None.

**Poster**

**489. Auditory Processing: Perception, Cognition, and Action I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 489.28/CC17

**Topic:** D.06. Audition

**Support:** Irish Research Council Postgraduate Scholarship Scheme

**Title:** Auditory attention detection in a non-stationary multi-speaker environment

**Authors: *E. TEOH**[1], E. C. LALOR[2]
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**Abstract:** Recently, it has been shown that attentional selection in a naturalistic multi-speaker environment can be robustly decoded from electroencephalography (EEG) (O'Sullivan et al., 2014). In particular, this is done by relating the acoustic envelope of a speech stimulus to the concurrently recorded EEG. Studies so far have nonetheless only considered this problem in the context of stationary speakers. In real life situations, this is usually not the case - speakers are typically more dynamic.
Here, we employ a paradigm in which the listener has to regularly alter their attended direction during the course of a trial. Specifically, participants are asked to attend to one of two speakers (located on their right and left) presenting continuous natural speech whilst EEG is recorded from their scalp. The speakers' perceived locations in space are swapped around at short intervals such that participants have to repeatedly vary their locus of attention to track their target speaker.
We show that decoding of the attended speaker is robust to the frequent changes in their location - the overall accuracy is comparable to previous studies. Additionally, we also investigate oscillatory measures of attention and suppression. In previous studies, it has been shown that EEG alpha band activity is lateralised according to the direction of attention. Consistent with these findings, computation of the alpha Attention Modulation Index (AMI; Wöstmann et al., 2016) by averaging of alpha (8 - 14Hz) power following each switch across all trials shows lateralisation over the occipital scalp area. Moreover, preliminary attempts for decoding attention using the AMI on a trial-by-trial basis lead to accuracies above the chance level.

**Disclosures:** **E. Teoh:** None. **E.C. Lalor:** None.

**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

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Columbia Research Initiatives in Science and Engineering

Gatsby Initiative in Brain Circuitry

**Title:** Spike-linked hemodynamic response function (HRF) switches sign and functional form between alert engagement in a task, and drowsiness

**Authors: *A. DAS**[1], M. M. B. CARDOSO[3], B. R. LIMA[4], Y. B. SIROTIN[2]
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**Abstract:** When interpreting hemodynamics-based measurements as in fMRI, the HRF is assumed to reflect neurovascular coupling to local neural responses (here, spiking). This coupling is believed to remain locally consistent although its strength can change between drowsy and alert states (Schölvinck et al. 2010). Here we tested if the HRF remained consistent even when switching between states of drowsiness and alert engagement in a task.
We recorded multi-unit spiking activity (MUA) simultaneously with intrinsic-signal optical images (specifically, blood volume) from macaque primary visual cortex (V1). The animal's task, which consisted of periodically holding fixation for a juice reward, elicits a powerful task-related hemodynamic response that entrains to task timing independent of visual stimulation (Sirotin and Das, 2009). We recorded extended sessions in total darkness other than the small (~2 arc min) fixation cue. The recordings thus included segments when the animal was actively engaged in the task, interspersed with segments when he shut his eye and appeared to drift asleep.
During the alert segments the measured hemodynamics was dominated by the task-related response, while the ongoing MUA showed a weak task-entrained modulation in response strength. During drowsy segments the hemodynamics showed large phasic increases in local blood volume while the MUA showed large, multi-second bursts. We used deconvolution to obtain the HRF linking the hemodynamics to the MUA over a moving window (typically 150 sec) sampling alert and drowsy segments. The 'drowsy' HRF resembled a standard causal HRF kernel predicting an increase in local blood volume following the spiking, with the typical times to peak and peak width. The 'alert' HRF was distinctly different, with an acausal temporal profile reflecting the periodic task timing, and a reversed sign predicting local decrease of blood volume following spiking. (This reversed sign is consistent with slight increase of spiking seen following the increased blood volume). Cross validation between the two epochs was poor: the mean of the 'drowsy' HRF kernels gave consistently good predictions (quantified by Pearson's r) over the drowsy segments, but gave incorrect phase-reversed predictions in the alert segments. Neurovascular control thus likely involves very different neural mechanisms in drowsy vs. alert engaged states. These results should have considerable bearing on our understanding of the HRF, and the interpretation of fMRI in terms of local neural activation.

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**Poster**

**490. Visual System: New Tools and New Views**

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**Topic:** D.07. Vision

**Support:** ELSC Post-Doctoral Fellowship Abroad

R01-EY025673

Intramural Research Program at NIMH

**Title:** Stimulus vignetting and coarse-scale biases for orientation in human visual cortex

**Authors: Z. N. ROTH**[1], D. J. HEEGER[2], *E. P. MERRIAM[1]
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**Abstract: Purpose:** Multivariate analyses are widely employed in human fMRI studies. But there is considerable controversy over what decoding analyses reveal about underlying neural architecture. We previously demonstrated that a coarse-scale bias for radial orientations in human primary visual cortex (V1) is both necessary and sufficient for orientation decoding (Freeman et al., 2011). It has been hypothesized that the radial bias is related to the edge of the stimulus aperture, rather than a neural preference for radial orientations (Carlson, 2014, Wang et al., 2014). We tested this possibility by measuring cortical activity with fMRI to oriented gratings modulated by two different apertures.
**Method:** Stimuli consisted of a carrier grating multiplied by a modulator. The carrier was a Cartesian sinusoidal grating that filled an annulus extending from 0.5 to 10 deg. The orientation of the stimulus changed every 1.5 s, cycling through sixteen evenly-spaced angles (0-180 deg) in 24 s. The modulator was a second sinusoidal grating that was constant throughout each fMRI run (i.e., it did not change orientation or phase). On half the runs, the modulator had an angular orientation, producing a series of ‘spokes’ centered on the fixation cross. On the other half of runs, the modulator had a radial orientation, producing a series of ‘rings’ emanating from the fixation cross. The fMRI data analysis characterized the preferred orientation for each voxel to the carrier grating. Five volunteers were scanned with a 3T Siemens Allegra at NYU (8-ch phased-array surface coil, 24 slices, voxel size 2×2×2 mm). Seven volunteers were scanned with a 7T Siemens Magnetom at NIH (32-ch coil, 54 slices, voxel size 1.2×1.2×1.2 mm).
**Results:** The majority of voxels in V1 exhibited robust and reliable orientation preferences to the carrier grating, confirming that fMRI responses in human V1 are selective for orientation. However, the orientation preference of most voxels were determined by the orientation of the modulator grating. For the radial modulator, voxels exhibited a radial bias. For the angular

modulator, voxels exhibited a tangential bias (i.e., rotated 90 deg from radial). We observed no evidence for orientation tuning that was unaffected by the orientation of the modulator grating. **Conclusions:** Ostensible orientation tuning in fMRI activity arises from interactions with the edge of the stimulus aperture.

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**Poster**

**490. Visual System: New Tools and New Views**

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EU grant 604102

**Title:** Viewing cortical processing in sensory space

**Authors: *A. T. MORGAN**[1], L. S. PETRO[2], L. MUCKLI[2]
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**Abstract: Introduction:**
Comparing information processing properties of different cortical areas is a fundamental challenge for systems neuroscience and can provide key insights to the interactions and information transformations executed by the brain. Information-based methods such as Representational Similarity Analysis (RSA; Kriegeskorte, at al. 2008) are powerful approaches that capitalize on multi-variate properties of neuroimaging signals to model the informational structure of brain areas. However, we show that examining model weights from V1 and V2 fMRI responses in visual space provides additional detail about retinotopically localized processing in each area compared to using RSA alone.
**Methods:**
We presented 24 partially occluded scenes to 18 participants and modelled V1 and V2 response differences in three image quadrants using RSA (Walther, et al. 2015). We projected models to visual space by weighting each voxel's population receptive field function (Dumoulin & Wandell, 2008) by its corresponding average model weight in each scene and summing across the visual field (Kok and de Lange, 2014; Thirion, et al. 2006). For comparison, we projected voxel response differences from the mean response to all images.
**Results:**
RSA model weight projections corresponded substantially more to visual features in the visible portions of scenes than response projections (Figure 1). In occluded portions of scenes, responses

did not vary much from their mean. However, model weight projections showed consistent retinotopic information sources across subjects, even in the absence of feedforward scene information, and these information sources differed between V1 and V2.

**Conclusions:**

We have shown that examining RSA models weights as visual space projections provides important detail about scene features that enable multi-voxel scene decoding. Importantly, this method is compatible with data from any sensory modality, and viewing weights in sensory space enables subject-, cortical area-, cortical layer-, task-, and computational model-based comparisons of information maps.

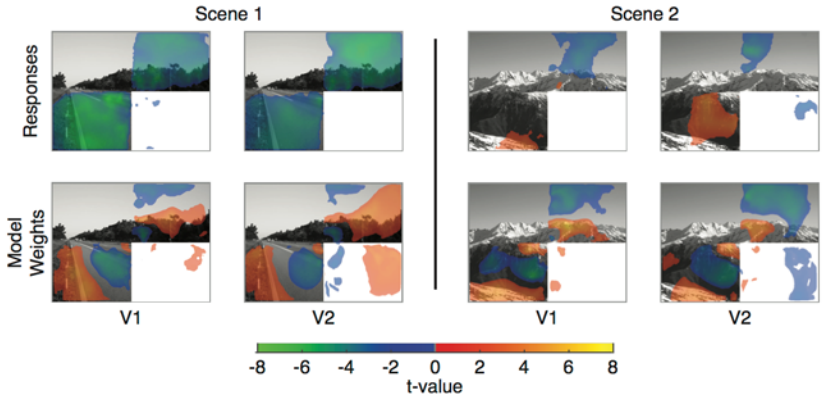


**Figure 1:** We calculated population receptive fields (pRF; Dumoulin & Wandell 2008) for V1 and V2 voxels from an fMRI dataset consisting of 18 subjects viewing 24 partially occluded visual scenes (Morgan, et al. 2016). For response projections (first row), voxel responses were projected by calculating a weighted average of all voxels' pRFs, where weights were each voxel's response amplitude with the mean response to all scenes removed. For model weight projections, the relative contributions to an LDA solution were averaged for each voxel (for significant classifications involving each scene) and weights were projected similarly to responses. In both projection types, a two-tailed t-test was conducted across subject maps at each pixel location to obtain t-value maps ($p < 0.05$ threshold). In response projections, warm colors show above-mean responses and cool colors show below-mean responses. In model weight projections, warm colors are visual areas where voxel activation is indicative of the respective scene and cool colors are areas where voxel activation is indicative of a different scene (across comparisons to 23 other scenes).

**Disclosures:** **A.T. Morgan:** None. **L.S. Petro:** None. **L. Muckli:** None.

**Poster**

**490. Visual System: New Tools and New Views**

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**Title:** Multidimensional encoding of structural brain connectomes: Building quantitative biological networks with preserved edge properties to study the visual white matter and brain aging

**Authors: *F. PESTILLI**[1], B. MCPHERSON[4], D. BULLOCK[5], A. I. AVENA KOENIGSBERGER[2], J. A. CONTRERAS[6], C. F. CAIAFA[7], O. SPORNS[3], A. J. SAYKIN[8]
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**Abstract:** The ability to map brain networks in living individuals is fundamental in efforts to chart the relation between brain and behavior in health and disease. We present a framework to encode brain connectomes and diffusion-weighted magnetic resonance data into multidimensional arrays. The framework goes beyond current methods by integrating the relation between connectome nodes, edges, white matter fascicles and diffusion data. We demonstrate the utility of the framework for in vivo white matter mapping and anatomical computing by evaluating more than 3,000 connectomes across thirteen tractography methods and four data sets in normal and clinical populations.
We show that this framework allows mapping connectivity matrices, edge anatomy, and microstructural properties of the white matter tissue in each connectome edge. The framework is based on statistical evaluation principles introduced with the Linear Fascicle Evaluation and virtual lesions methods (LiFE; Pestilli et al., 2014). In short, instead of building networks by relying uniquely on the terminations of fascicles into the cortex, we exploit the full measured signal available for each connectome edge and node by extracting a forward-prediction of the biological tissue properties of the edge. We validated the framework by comparing results with measures standard connectome measures (fiber count and density). To do so, we generated ten repeated-measures connectomes in each individual brain in various datasets, using different tracking methods. For each connectome estimated in an individual brain, we computed the mean network clustering coefficient across repeated measures. We demonstrate the high reliability of the clustering measures in individuals. We also demonstrate profound differences in connectomes across brains, beyond what can be captured using standard measures (fiber density). We also show that the proposed method is highly sensitive to differences between individuals by improving subject classification into various diagnostic groups. Finally, we show that the framework is useful in clarifying fundamental properties of the human visual white matter as well as identifying useful network science biomarkers for predicting degenerative changes in the Alzheimer's brain.

We publish the method with software compatible with data from the Human Connectome Project, the Alzheimer Disease Neuroimaging Initiative, and Indiana Alzheimer Disease Center Data. The software integrates the Brain Connectivity Toolbox and is available open source GitHub.com/brain-life and stand-alone at hub.docker.com/u/brainlife.

**Disclosures:** **F. Pestilli:** None. **B. McPherson:** None. **D. Bullock:** None. **A.I. Avena Koenigsberger:** None. **J.A. Contreras:** None. **C.F. Caiafa:** None. **O. Sporns:** None. **A.J. Saykin:** None.

**Poster**

**490. Visual System: New Tools and New Views**

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**Topic:** D.07. Vision

**Support:** NWO Vidi Grant 13339

**Title:** Cortical depth and profile modeling for laminar MRI

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**Abstract:** Recent advances in ultra-high field MRI have enabled to probe intra-cortical details of structure and function in living humans at sub-millimetric resolutions. The laminar structure of the neocortex provides a natural coordinate system for intra-cortical mapping, with cortical layers defining depth and cortical profiles following the vertical organization of cortical columns, intra-cortical vasculature, and incoming white matter fibers. Unfortunately, the best achievable resolution in MRI is still very coarse with regard to these structures and cortical depth and profiles need to be defined from macro-anatomical information, namely the white matter boundary and pial surface.
Here, we present and compare computational strategies to 1) define cortical depth with a distance-preserving or volume-preserving model, 2) measure intra-cortical features along cortical profiles with local profiles and ROI-based spatial general linear model (GLM) methods, and 3) smooth data along cortical layers. Unlike current surface-based methods, our approach works directly in volumetric space and samples all available data according to their partial volume estimates. To study the impact of different modeling strategies on intra-cortical data, we applied the methods to two ultra-high resolution MRI data sets both acquired with a T2*-weighted 3DEPI sequence on a Phillips 7T scanner with a dedicated 32-channel surface receive coil. First,

a 0.3 mm isotropic resolution anatomical image of the occipital pole was acquired on a single subject, showing the Stria of Gennari as well as many intra-cortical draining veins. Second, a 0.55 mm isotropic resolution functional scan was acquired in four subjects while participants viewed an alternating left and right sided dartboard pattern to induce differential activation in visual areas.
Our results show that a volume-preserving model with a spatial GLM provides the best fit to small regions of interest, compared to pooling individual profiles. The distance-preserving depth model introduces a widening and shift of intra-cortical profiles in curved regions. Local profiles have lower contrast, however the limited resolution along cortical depth impacts the stability of the GLM estimation. While laminar smoothing did not increase stability and did reduce contrast, we show that a approximation of the GLM by partial volume mixtures removes the instability entirely while retaining the higher contrast. Taken together, these results indicate that the estimation of subtle intra-cortical signal in anatomical and functional MRI requires carefully optimized cortical depth and profile modeling strategies.

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**Poster**

**490. Visual System: New Tools and New Views**

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**Topic:** D.07. Vision

**Support:** EU Grant 641805

**Title:** Linear responses across lamina in early visual cortex using sub-millimetre resolution fMRI

**Authors: *J. VAN DIJK**[1,2], A. FRACASSO[1,2,3], S. O. DUMOULIN[1,2]
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**Abstract:** A fundamental assumption of nearly all fMRI methods is that the relationship between local neuronal activity and the fMRI signal is linear. Experimental evidence supports this notion for fMRI at conventional resolutions (>1mm isotropic). Recent advances in ultra-high field MRI (7T) allowed for high-resolution (sub-millimetre) fMRI. A novel and promising application of sub-millimetre fMRI is laminar imaging, i.e. measuring fMRI-responses across the thickness of the cortex, in particular to dissociate feed forward and feedback signals as they arrive at different lamina. However, known blood supply differences across lamina strongly affect the signal and may also affect the linearity of the signal over cortical lamina.
We collected fMRI data at 0.7mm isotropic, using a GE 3D-EPI sequence on a Philips 7T

scanner with 32-channel surface receive coils. We additionally collected 5 extra volumes with the opposite phase encoding direction to correct for geometrical distortions induced by the static magnetic field. Participants viewed sine-wave gratings in a circular aperture (9.5deg diameter) for 12 seconds, with 5%, 20%, and 80% contrast. We computed percentage response amplitude for each contrast. The statistical maps were distortion-corrected, and coregistered to a high-resolution (0.65mm isotropic) anatomy. Computational cortical layers were defined using an equivolume approach. We selected V1 voxels using independent visual field mapping.
We obtained strong responses in V1 for all contrasts and for all subjects. Signal amplitudes increased with increasing stimulus contrast. This increase was non-linear, as expected from the known non-linear contrast response function in the visual cortex. The signals also increased systematically as a function of cortical lamina, where responses increased towards the pial surface. Having taken into account the non-linear contrast response function, the laminar profiles for each contrast could be accurately modelled as a scaled version of the response to any other contrast, suggesting strong linearity of response profiles across lamina.
Our results provide evidence for a linear response function across lamina, despite known blood supply differences across lamina. This suggests that the assumption that the BOLD response is linear holds not only for regular, but also for sub-millimetre fMRI and laminar imaging.

**Disclosures:** **J. Van Dijk:** None. **A. Fracasso:** None. **S.O. Dumoulin:** None.

**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

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**Title:** A second-order orientation-contrast stimulus for population-receptive-field-based retinotopic mapping

**Authors: *F. YILDIRIM**[1,2], J. CARVALHO[1], F. W. CORNELISSEN[1]
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**Abstract:** Visual field or retinotopic mapping is one of the most frequently used paradigms in fMRI. It uses activity evoked by position-varying high luminance contrast visual patterns presented throughout the visual field for determining the spatial organization of cortical visual areas. While the advantage of using high luminance contrast is that it tends to drive a wide range of neural populations – thus resulting in high signal-to-noise BOLD responses – this may also be a limitation, especially for approaches that attempt to squeeze more information out of the BOLD response, such as population receptive field (pRF) mapping. In that case, more selective stimulation of a subset of neurons – despite reduced signals – could result in better characterization of pRF properties. Here, we used a second-order stimulus based on local differences in orientation texture – to which we refer as orientation contrast – to perform retinotopic mapping. Participants in our experiment viewed arrays of Gabor patches composed of a foreground (a bar) and a background. These could only be distinguished on the basis of a difference in patch orientation. In our analyses, we compare the pRF properties obtained using this new orientation contrast-based retinotopy (OCR) to those obtained using classic luminance contrast- based retinotopy (LCR). Specifically, in higher order cortical visual areas such as LO, our novel approach resulted in non-trivial reductions in estimated population receptive field size of around 30%. A set of control experiments confirms that the most plausible cause for this reduction is that OCR mainly drives neurons sensitive to orientation contrast. We discuss how OCR – by limiting receptive field scatter and reducing BOLD displacement – may result in more accurate pRF localization as well. Estimation of neuronal properties is crucial for interpreting cortical function. Therefore, we conclude that using our approach, it is possible to selectively target particular neuronal populations, opening the way to use pRF modeling to dissect the response properties of more clearly-defined neuronal populations in different visual areas.

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**Poster**

**490. Visual System: New Tools and New Views**

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**Program#/Poster#:** 490.08/CC25

**Topic:** D.07. Vision

**Support:** MRC Grant MR/K014382/1

**Title:** Geostatistical mapping of high-resolution fMRI reveals size and arrangement of high-signal clusters of BOLD activity in visual cortex

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**Abstract:** Functional topography is present throughout the cerebral cortex, often in the form of columns or clusters of neurons with similar functional properties within identified cortical regions. Most of the evidence for these structures comes from work with non-human species. Using 7-Tesla functional MRI, with gradient-echo echo-planar imaging at 0.75 mm isotropic resolution in human visual cortex, we used a phase-encoded paradigm in which binocular stereoscopic depth was changed steadily over time from -0.21 to +0.21 degrees disparity in ramped sawtooth waveform. The BOLD signals showed significant clustering and topographical structure in extrastriate visual areas V2, V3 and V3a.
The definition of clustered structures is frustrated by the presence of a background of local spatial correlations in the BOLD signal across the cortical surface. This structured background, which we term 'neural dust', is a form of noise that imposes a fundamental limit on the detection of clustering and topography. We apply a novel analysis approach that quantifies these background, spatial correlations. We measure the variogram, a distant-dependent measure of variance, which is applicable to discrete pairs of sample points and analogous to the autocorrelation function for continuous data. For two observations $Z_i$ and $Z_j$ at points $u = (x_i, y_i)$ and $v = (x_j, y_j)$ the variogram $\gamma$ is given by $2\gamma(u, v) = var\ (\ Z(u) - Z(v)\ )$, where *var* is the variance. We divide the population of voxels into groups having low- and high-signal coherence (< 0.3 or >= 0.3 correlation with the disparity waveform). For low-signal voxels, the variogram rises to a plateau as distance increases. The range over which the variogram rises quantifies the spatial correlations, which limit the practical resolution of the MR images to approximately 1mm (Gaussian half-width), closely similar to the physical limit predicted for the imaging system. Variogram analysis allows reliable identification of high-signal clusters of activation in the human cortex. We show that high-signal voxels modulated by stimulus changes of binocular stereoscopic depth occur in clusters, resulting in a systematic mapping of disparity-defined depth in regions of human early visual cortex. These high-signal clusters, on a scale as large as 12-15mm, were reliably identified across the cortical surface of all subjects tested, predominantly within visual cortical area V3A. These methods provide an objective approach for defining the size and locations of clusters of cortical fMRI activation to enable comparison with invasive methods that are less affected by noise.

**Disclosures:** **A.J. Parker:** A. Employment/Salary (full or part-time):; University of Oxford, UK. 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.; Medical Research Council, UK. **H. Bridge:** A. Employment/Salary (full or part-time):; Oxford University, UK. 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.; Royal Society and Medical Research Council.

**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

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**Program#/Poster#:** 490.09/CC26

**Topic:** D.07. Vision

**Support:** DFG BA4914/1-1

DFG EXC307

Max Planck Society

**Title:** Detecting eye-selective fMRI activity in the human primary visual cortex at 3T and 9.4T

**Authors: *N. ZARETSKAYA**[1,2,4,6], J. BAUSE[5], J. R. POLIMENI[7,8], K. SCHEFFLER[5,3], A. BARTELS[1,2,4,6]
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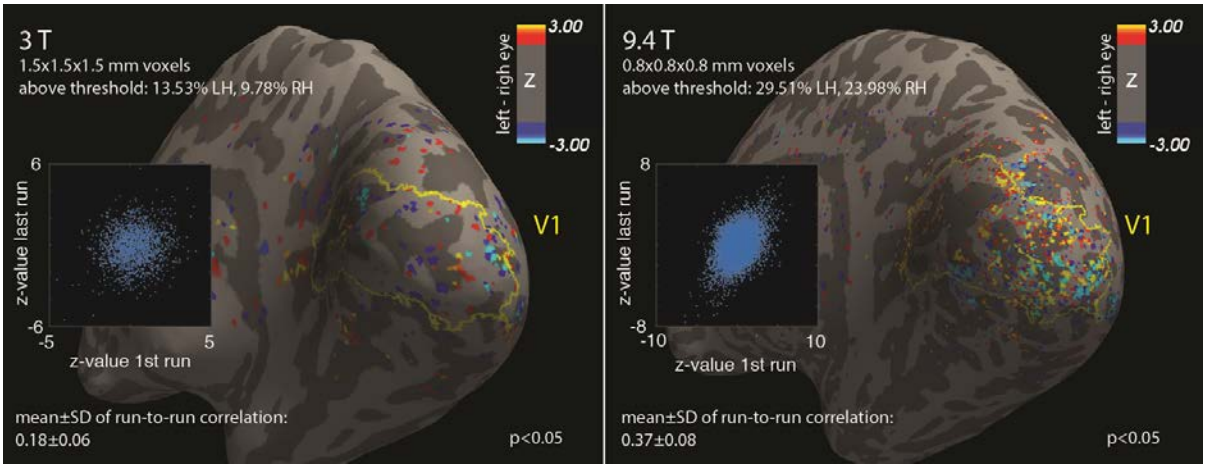
**Abstract: Introduction**
The primary visual cortex of humans contains patches of neurons responding preferentially to stimulation of one eye (ocular dominance columns) (Adams et al., 2007). The majority of previous fMRI studies reporting eye-specific activity in V1 used magnetic field strengths of 4 T and higher (Cheng et al., 2001; Yacoub et al., 2007; Nasr et al., 2016). However, there have been reports of reliable eye-selective activations at 3 T (Haynes et al., 2005). Here we present preliminary results on the ability to detect eye-selective V1 activity using high-resolution fMRI at 3 T and 9.4 T.
**Methods**
BOLD signal of one healthy adult volunteer was measured at 3 T and 9.4 T using 2D GE-EPI (3 T: 1.5mm isotropic resolution, TR/TE/matrix/GRAPPA = 1720/30/128x128x24/R=3, 873 volumes; 9.4 T: 0.8mm isotropic resolution TR / TE / matrix / GRAPPA=2 s / 22 ms /230×230×40 / R=5, FLEET autocalibration (Polimeni et al., 2016), 900 volumes). Each eye was stimulated separately with a checkerboard flickering at 2 Hz for 18 s with 18 s breaks, viewed through a prism stereo display (Schurger, 2009). Structural scans (1mm$^3$ for 3 T and 0.6 mm$^3$ for 9.4 T) were acquired in each session for cortical surface reconstruction.
All analyses were performed using FreeSurfer 6.0 and FS-FAST (Fischl, 2012). Functional data

were motion-corrected, co-registered to the anatomy using boundary-based registration (Greve and Fischl, 2009) with 6 DOF for 3 T and 9 DOF locally constrained to V1 for 9.4 T, and analyzed using voxel-wise GLM with left eye, right eye and baseline regressors. Surface-based prediction of V1 location (Hinds et al., 2008) was used to label volume voxels belonging to V1 gray matter, and z-statistics of the contrast “left eye vs. right eye” were extracted from those voxels.

**Results**

We observed a more than two-fold increase in the percentage of eye-selective voxels and in run-to-run correlation of eye preference at ultrahigh field.




**Conclusion**

Increase in spatial resolution and improved BOLD point spread function at 9.4T allows for better detection of eye-selective signal related to ocular dominance columns.

**Disclosures:** **N. Zaretskaya:** None. **J. Bause:** None. **J.R. Polimeni:** None. **K. Scheffler:** None. **A. Bartels:** None.

**Poster**

**490. Visual System: New Tools and New Views**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 490.10/CC27

**Topic:** D.07. Vision

**Title:** Improvements for periodic intrinsic signal imaging of mouse visual cortex

**Authors: *J. BOLZ**[1], M. TEICHERT[2]
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**Abstract:** One major aspect of neuroscience is to characterize responses of sensory cortices evoked by external stimuli. A well-established technique allowing such investigation is optical imaging based on intrinsic signals. It enables non-invasive measurements of cortical activity over large brain areas with a high spatial resolution (Kalatsky and Stryker, 2003). Intrinsic imaging is a frequently used method for characterization and measurement of stimulus evoked responses e.g. in the primary visual cortex in mice (Kaneko et al., 2008; Isstas et al., 2017). For stable and reproducible results it is particularly important to control the anesthetic state of the animal during the recording session. Here, we examined how cortical maps are influenced by cardiopulmonary alterations. For this, we increased the concentration of isoflurane stepwise from 0.5% to 1.25% during one imaging session. At each step we measured the respiration rate (RR), the heart rate (HR) and the amplitude of visual cortex responsiveness evoked by visual stimulation. Our results demonstrate that the RR is a suitable and reliable indicator for anesthetic depth under isoflurane anesthesia which highly correlates with the strength of elicited visual cortex activity at the level of individual animals. In contrast, the HR appeared to be only a weak indicator for the anesthetic depth. Furthermore, we developed a novel technique which enables to determine the cortical visual acuity and contrast sensitivity using periodic imaging in a fast and simple manner. To validate this new method, we first determined contrast sensitivity and visual acuity in the visual cortex dependent behavioral visual water task (VWT). Then, we measured these attributes of vision with our adapted intrinsic imaging method in the same mice. Strikingly, our results showed that the data obtained in the VWT and by intrinsic imaging were almost identical, even at the level of individual animals. In conclusion, compared to established behavioral or electrophysiological methods for the determination of visual performance and perception in rodents which are time consuming or require complex and invasive surgeries (Porciatti et al., 1999; Prusky et al., 2000) our novel approach is quasi non-invasive and speeds up the experimental time to about 2 h. Taken together, we show that periodic intrinsic imaging is a powerful method for determining reliable values of visual perception in mice which provides clear advantages above conventional methods to measure mouse visual perception.

**Disclosures: J. Bolz:** None. **M. Teichert:** None.

**Poster**

**490. Visual System: New Tools and New Views**

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**Topic:** D.07. Vision

**Support:** BRAIN Initiative Grant 1U01MH109146-01

**Title:** Anion channelrhodopsin suppresses neural activity in awake monkeys

**Authors: *S. DEBES**[1], A. R. ANDREI[2], R. JANZ[3], V. DRAGOI[4]
[1]Neurobio. and Anat., Univ. of Texas At Houston, Houston, TX; [2]Neurobio. & Anat., McGovern Med. Sch., Houston, TX; [3]UT-Houston Med. Schl, Houston, TX; [4]Dept Neurobiol/Anat, Univ. of Texas at Houston Dept. of Neurobio. and Anat., Houston, TX

**Abstract:** Optogenetic methods allow for causal, cell specific perturbation of neuronal circuits. While ChR2 is widely used as a cation channelrhodopsin, we have yet to find an anion channelrhodopsin with similarly robust qualities for optogenetic suppression. Effectively suppressing neural firing would allow the investigation of neuronal circuit function in behaving animals. In this study we used a novel anion channelrhodopsin, *Gt*ACR2 to suppress neural responses of glutamatergic cells in the primary visual cortex (V1) of two awake, behaving rhesus macaque monkeys (*macaca mulatta*). *Gt*ACR2 is a light-gated chloride channel, packaged in a lentivirus vector with a CaMKIIα promoter and injected into multiple sites of V1. After waiting six weeks for the virus to express, laminar probes were used to collect single and multi-unit activity. Recordings were performed in parallel with optical inactivation using a laser-connected fiber optic cable. Monkeys completed a contrast detection task in which they maintained fixation on a central point while gratings of various contrasts were presented at parafoveal locations. Animals signaled the presence or absence of a stimulus. On half of the trials, optical stimulation was continuously presented during the entire stimulus presentation (300 ms). Across cells, we found that neuronal firing during stimulus presentation was suppressed by an average of 5.7 spikes per second (± 4.1) during the laser trials compared to control trials. Additionally, we found that the largest response suppression (laser vs. control) was 9.3 spikes per second (± 4.7); this difference was statistically significant ($P$=0.0058, Student's t-test). The largest suppression magnitude occurred 221.8 ms (± 16.3) after laser onset, however, this difference did not return to baseline until 258.8 ms (± 27.6) after laser offset. Overall, our results indicate that *Gt*ACR2 is an adequate tool for optogenetic suppression *in vivo* in the non-human primate brain.

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**Poster**

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**Topic:** D.07. Vision

**Support:** Howard Hughes Medical Institute

**Title:** Neural signatures of dynamic stimulus selection in *Drosophila*

**Authors: *Y. SUN**, A. NERN, R. FRANCONVILLE, H. DANA, E. R. SCHREITER, L. L. LOOGER, K. SVOBODA, D. S. KIM, A. M. HERMUNDSTAD, V. JAYARAMAN
HHMI Janelia Res. Campus, Ashburn, VA

**Abstract:** Many animals orient using visual cues, but how a single cue is selected from among many is poorly understood. *Drosophila melanogaster* are known to display a wide variety of innate and learned visual behaviors, including visually guided spatial navigation. Here we show that ring neurons—central brain neurons implicated in compass navigation—display a form of visual stimulus selection. By using *in vivo* two-color two-photon imaging with genetically encoded calcium indicators GCaMP6f and jRGECO1a, we quantitatively compared visual responses of individual ring neurons to those of their upstream partners. Ring neurons inherit their simple-cell-like receptive fields from these upstream inputs. Visual responses of both populations were systematically suppressed in the presence of an identical stimulus presented in parts of the contralateral visual field, but this suppression was more pronounced in the ring neurons. The spatial profile of contralateral suppression was consistent with inhibition arising from the summation of the receptive fields of the identical population of neurons on the contralateral side. Finally, the strength of this suppression depended on when the contralateral stimulus had been presented, an effect stronger in ring neurons than their upstream inputs. The history-dependent effect on the temporal structure of ring neuron responses, which was well modeled by a simple biphasic filter, may determine how landmarks are selected as references for the fly's internal compass. Our approach also highlights how two-color calcium imaging can be used to localize the origins of sensory transformations across synaptically connected neural populations.

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**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 490.13/CC30

**Topic:** D.07. Vision

**Title:** Receptive field estimation from spikes using models of calcium dynamics

**Authors: *P. LEDOCHOWITSCH**, N. CAIN, R. IYER, S. DURAND, L. HUANG, L. LI, J. SIEGLE, X. JIA, G. OCKER, D. MILLMAN, K. LEPAGE, H. ZHENG, S. OLSEN, C. REID, S.

MIHALAS, S. DE VRIES, M. BUICE
Allen Inst. for Brain Sci., Seattle, WA

**Abstract:** Historically, most studies of receptive fields were undertaken using electrophysiology, with a notable, recent shift towards calcium imaging as a method of choice. Extracellular electrophysiology and $Ca^{2+}$ imaging both constitute noisy observations of the underlying neural activity. However, the statistical properties of the raw signals, as well as the sources and effects of the introduced noise are quite distinct. To interpret receptive field maps derived from $Ca^{2+}$-imaging in the context of existing literature, it is therefore crucial to understand how these differences are reflected in the detectability and properties of receptive fields derived from extracellular spike trains as compared to those obtained from $Ca^{2+}$-dependent fluorescence traces, respectively. To address this issue, we first compute receptive fields from extracellular spike trains recorded in mouse V1 directly using the spike-triggered average. In a second step, we auto-calibrate a biophysical (forward) model that relates spiking activity to observed fluorescence (MLspike, [1]) on data from the Allen Brain Observatory (http://observatory.brain-map.org/visualcoding/), a public resource, which provides a standardized in vivo characterization of single neuron activity in the mouse visual cortex based on $Ca^{2+}$-imaging. Following this calibration, we then compute model calcium activity for above spike trains. The obtained synthetic fluorescence traces are subsequently analyzed using a method developed for mapping of classical receptive fields in the Allen Brain Observatory, based on responses to a locally sparse noise stimulus.
We find that this analysis readily yields receptive fields that largely agree with those identified directly from the electrophysiological recordings, and investigate the sensitivity of the obtained receptive field structure to the parameterization of the forward calcium model. In the future, this data-driven modeling approach may provide a Rosetta Stone for receptive field comparison across recording modalities, as well as inspire improvements to algorithmic receptive field fitting procedures.
[1] Deneux, T., Kaszas, A., Szalay, G., Katona, G., Lakner, T., Grinvald, A., et al. (2016). Accurate spike estimation from noisy calcium signals for ultrafast three-dimensional imaging of large neuronal populations in vivo. Nature Communications, 7, 12190 EP -. http://doi.org/10.1038/ncomms12190

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**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 490.14/CC31

**Topic:** D.07. Vision

**Title:** Measuring cellular-level interactions across multiple areas in mouse visual cortex using parallel silicon probe recordings

**Authors: *J. H. SIEGLE**, X. JIA, D. J. DENMAN, R. DIETZMAN, C. KOCH, S. R. OLSEN
Allen Inst. for Brain Sci., Seattle, WA

**Abstract:** The Allen Institute has performed an extensive characterization of the response properties of cells in individual visual areas using 2-photon imaging of genetically encoded calcium sensors (http://observatory.brain-map.org/visualcoding). But to understand how the visual system achieves dynamic coordination between brain regions, it is necessary to monitor the activity of multiple areas simultaneously with single-spike temporal resolution. To study this, we built a rig capable of targeting arrays of extracellular electrodes to retinotopically matched regions of mouse cortical visual areas, including AM, PM, RL, LM, and V1. Using miniature 3-axis linear stages from New Scale Technologies, we are able to align up to six 384-channel Neuropixels probes to area maps obtained via intrinsic signal imaging (wild-type mice) or though-skull widefield imaging (Emx1-IRES-Cre; Camk2a-tTA; tetO-GCaMP6s mice). We recorded spiking activity across all 6 cortical layers in response to a variety of visual stimuli, including drifting gratings, white noise, and natural scenes. We measured functional connectivity between layers and areas using cross-correlograms, mutual information, conditional firing rate correlations, and Granger causality. In the future, we plan to scale this paradigm into a pipeline capable of collecting highly standardized experiments across large numbers of mice.

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**Poster**

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**Topic:** D.07. Vision

**Support:** DoI/IBC Contract D16PC0004.

**Title:** High contrast tissue preparation for large scale serial section electron microscopy of mice and humans

**Authors: *M. M. TAKENO**[1], J. BUCHANAN[1], A. BLECKERT[1], T. DAIGLE[2], R. P. GWINN[4], C. S. COBBS[4], H. ZENG[3], N. M. DA COSTA[1]
[1]Neural Coding, [2]Transgenic Technol., [3]Structured Sci., Allen Inst. For Brain Sci., Seattle, WA; [4]Swedish Neurosci. Inst., Seattle, WA

**Abstract:** Morphology and connectivity are two defining features of cell types. We use large-scale Transmission Electron Microscopy (TEM) to characterize such features of neocortical neurons. In this study we describe our efforts to create samples that allow the reconstruction of the wiring diagram of neocortical circuits at synapse resolution of mice and humans, as well as characterization of their cell types.
We developed *en bloc* staining protocols to prepare tissue for large-scale (> 1 $mm^3$) serial-section TEM. We are incorporating methodology from different reduced osmium (rOTO) protocols (Hua et al., Nature Communications 2015), to see what permutations will break the "osmium shell" caused by the formation of physical barriers to diffusion. These permutations include the addition of formamide, substitution of pyrogallol for thiocarbohydrazide (Mikula and Denk, Nature Methods 2015), and lengthening of the OTO (osmium-thiocarbohydrazide-osmium) step. We demonstrate the use of this protocol in both perfused mouse visual cortex and from drop-fixed human surgical biopsies.
Circuit-level electron microscopy connectivity studies would also benefit from cell-type specific markers that would link morphological descriptions to genetic tools. The Allen Institute has developed a transgenic mouse reporter line (Ai133) expressing the genetically encoded peroxidase APEX2. When bred with the Scnn1a-Tg3-Cre driver line, APEX2 is expressed in the cytosol of select neurons in layer 4 of primary visual cortex. Combining the APEX2 protocol with our refined *en bloc* rOTO staining protocol produced tissue with high contrast membranes and cytosolic contrast in the genetically tagged cells, permitting auto segmentation of the final image stacks.
All samples showed well-preserved ultrastructure with well-defined membranes, clear synaptic structure, and high contrast. It is critical to avoid on section staining of the serial thin sections on films mounted on copper grids or grid tape. These protocols eliminate the need to post section stain and avoid the risk of contamination by precipitate and dirt. The high contrast enables the short imaging times necessary for our large-scale, high throughput imaging method.

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**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

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**Program#/Poster#:** 490.16/CC33

**Topic:** D.07. Vision

**Support:** NIDA Grant R01DA036909

**Title:** New TIGRE 2.0 transgenic reporters for functional analysis of neural circuits

**Authors: *T. L. DAIGLE**, L. SIVERTS, H. GU, M. MILLS, M. WALKER, E. GARREN, L. GRAY, L. MADISEN, B. TASIC, H. ZENG
Allen Inst. For Brain Sci., Seattle, WA

**Abstract:** Modern genetic approaches have allowed for unprecedented access to diverse types of neurons within the mammalian brain and have greatly facilitated the study of their function. In parallel, the development of highly sensitive sensors and optical tools has enabled the labeling of diverse cell types, the perturbation of neuronal activity with precise temporal control and the visualization of distinct neural states. Over the last several years we have developed multiple gene expression platforms in mice using various molecular genetic approaches that achieve high levels of fluorescent proteins, sensors, and optogenetic tools within selective cell populations, defined largely by unique Cre driver lines. The TIGRE locus (Zeng, H et al., PLOS Genetics 2008) represents one of our favored platforms for transgenic production because it is uniquely permissive for tetracycline-inducible regulatory elements and because it achieves transgene expression comparable to that achieved with viral methods. Here we will report our newest TIGRE 2.0 Cre-dependent reporter lines that were generated using our previously published strategy (Madisen L et al., Neuron, 2015). This new collection of reporters include tools that will enable optical physiology, optogenetics, and sparse labeling of genetically defined cell populations. TIGRE 2.0 reporters offer several key advantages compared to our first generation of TIGRE lines such as a more simplified breeding strategy and robust transgene expression within different populations of interneurons and neuromodulatory cell types. Anatomical and functional data for several TIGRE 2.0 reporter lines will be presented and the lines currently under development will be described. These novel transgenic lines will greatly expand the repertoire of high precision genetic tools available to effectively identify, monitor, and manipulate distinct cell types within the mammalian brain.

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**Poster**

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**Program#/Poster#:** 490.17/DD1

**Topic:** D.07. Vision

**Support:** Paul G. Allen Family Foundation

**Title:** Cell-type-dependent relationship between *In vivo* calcium events and spiking activity in transgenic mouse lines

**Authors: U. KNOBLICH**, *L. HUANG, P. LEDOCHOWITSCH, M. A. BUICE, J. WATERS, C. REID, C. KOCH, H. ZENG, L. LI
Allen Inst. for Brain Sci., Seattle, WA

**Abstract:** Genetically encoded calcium indicators (GECIs) have been widely used with two-photon (2-p) imaging to report action potentials (spikes) within local populations of neurons in vivo. However, the relationship between observed calcium events and spiking activity is not yet fully understood, making it difficult to link these studies to the large body of existing knowledge about neuronal activity. This spike-to-calcium transfer function depends on several factors including the properties of the GECIs, the neuronal cell-types expressing GECI (due to differences in intracellular calcium dynamics), GECI expression level, and the behavioral state of the animal (due to changes in calcium dynamics, e.g. by neuromodulators). Recent advancement in transgenic mouse lines offers better opportunities, compared with the viral expression, to achieve more uniform expression of GECIs in genetically defined populations of neurons, enabling a more straightforward comparison of activity across cells and animals. Using our newly developed intersectional transgenic mouse lines expressing GCaMP6f or GCaMP6s in a Cre-dependent manner, we perform concurrent 2-p calcium imaging and 2-p targeted cell-attached recordings in the same neurons to simultaneously measure spiking and calcium activity to directly characterize their transfer function. These results will be beneficial for interpreting existing as well as future calcium imaging data such as the output of the Allen Institute's Allen Brain Observatory.

**Disclosures: U. Knoblich:** None. **L. Huang:** None. **P. Ledochowitsch:** None. **M.A. Buice:** None. **J. Waters:** None. **C. Reid:** None. **C. Koch:** None. **H. Zeng:** None. **L. Li:** None.

**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 490.18/DD2

**Topic:** D.07. Vision

**Support:** Gatsby Charitable Trust

NIH Grant EY022577

**Title:** Recording from large ensembles of neurons with high-density electrophysiology and two-photon calcium imaging in primate primary visual cortex

**Authors: *A. K. GARG**[1,2], P. LI[1], E. M. CALLAWAY[1]
[1]Systems Neurobio. Labs., Salk Inst. for Biol. Studies, LA Jolla, CA; [2]Neurosciences Grad. Program, UCSD, La Jolla, CA

**Abstract:** Decades of previous work have revealed the functional and anatomical organization of primate primary visual cortex (V1) at the level of cortical layers and columns. However, recent technological advances in extracellular electrophysiology and two-photon calcium imaging have allowed for investigation of more detailed cortical organization at the cellular level. We aim to develop and further refine approaches to link large ensembles of neurons in V1 to their laminar identity, cell types, functions, and connectivity. In this study, we demonstrate the ability of high-density Neuropixels electrode arrays and two-photon calcium imaging using GCaMP6f to increase our understanding of the principles and mechanisms by which large populations of neurons transform sensory input to give rise to patterns of neuronal activity in macaque V1. Integrating multiple imaging and recording technologies enables us to perform detailed studies revealing computational and organizational principles of functional cortical connectivity.
Using next-generation Neuropixels electrode arrays, we demonstrate the ability to simultaneously record from 50-100 V1 neurons across all cortical layers. In these experiments, we present a series of chromatic and achromatic visual stimuli consisting of stationary and moving gratings, which allows us to characterize cellular receptive fields of a wide array of cell types. Simultaneously recording from large ensembles of neurons enables us to use reverse correlation and cross-correlation analyses to reveal circuit mechanisms between functionally connected pairs or groups of neurons. Combining these results with current source density (CSD) analysis, in which we assign a laminar identity to each recorded neuron, enables us to reveal the laminar organization of color-responsive neurons in macaque V1.
In combination with our work using extracellular electrophysiology, we robustly express GCaMP6f in V1 using the TET-Off inducible gene expression system, allowing simultaneous imaging of calcium responses from hundreds of neurons. Using these results, we can align the calcium imaging responses with postmortem cytochrome oxidase staining to identify the locations of blobs and inter-blobs, and compare the differences between neuronal activity in each of these locations in response to a variety of visual stimuli.

**Disclosures:** **A.K. Garg:** None. **P. Li:** None. **E.M. Callaway:** None.

**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 490.19/DD3

**Topic:** D.07. Vision

**Support:** HFSP Long-Term Fellowship LT000769/2015

**Title:** Whole-brain functional ultrasound imaging in awake mice reveals the brain regions processing retina-encoded visual motion

**Authors: *E. MACÉ**[1], G. MONTALDO[2], S. TRENHOLM[1], C. COWAN[1], A. URBAN[2], B. ROSKA[1]
[1]Friedrich Miescher Inst., Basel, Switzerland; [2]Lab. of neural circuits, NERF, IMEC, VIB, KU Leuven, Leuven, Belgium

**Abstract:** Visual motion is encoded both within the retina and in higher visual areas [1]. Direction selective cells in the retina encode visual motion along the four cardinal directions [2] and drive specific behaviours such as the optokinetic reflex [3]. However, the system of brain regions that process retina-encoded direction selective signals is not well understood.
In order to reveal this system we used functional ultrasound imaging [4] to record activity across the whole brain of awake mice and parsed the signals into distinct brain regions. When wild type mice were stimulated with visual motion along the four cardinal directions, a stimulus that evokes the optokinetic reflex, an extensive set of brain regions was activated. We clustered brain regions based on response properties into functional groups: symmetrically responsive, direction selective, anti-correlated with visual motion stimulation or exhibiting different responses across hemispheres.
To find brain regions whose activity depends on retina-encoded horizontal direction selective signals, we specifically perturbed the detection of horizontal motion in the retina using *FRMD7* mutant mice [5] and compared whole brain activity maps across wild type and mutant mice. In *FRMD7* mutant mice, visual stimulation evoked no horizontal optokinetic reflex. Furthermore, activity in spatially distributed brain regions was significantly reduced during horizontal motion. The vertical optokinetic reflex and the activity in brain regions activated by vertical motion did not change.
Thus we reveal a brain-wide system of nuclei that process retina-encoded horizontal motion. Furthermore, we show that whole-brain functional ultrasound imaging can identify brain regions affected by circuit perturbations in awake mice.

**References:**

**1.** Hillier, D. *et al.* Causal evidence for retina dependent and independent visual motion computations in mouse cortex. *Nat Neurosci (in press)*
**2.** Vaney, D. I., Sivyer, B. & Taylor, W. R. Direction selectivity in the retina: symmetry and asymmetry in structure and function. *Nat. Rev. Neurosci.* **13,** 194-208 (2012).
**3.** Yoshida, K. *et al.* A key role of starburst amacrine cells in originating retinal directional selectivity and optokinetic eye movement. *Neuron* **30,** 771-780 (2001).
**4.** Macé, E. *et al.* Functional ultrasound imaging of the brain. *Nat. Methods* **8,** 662-664 (2011).
**5.** Yonehara, K. *et al.* Congenital Nystagmus Gene FRMD7 Is Necessary for Establishing a Neuronal Circuit Asymmetry for Direction Selectivity. *Neuron* **89,** 177-193 (2016).

**Disclosures: E. Macé:** None. **G. Montaldo:** None. **S. Trenholm:** None. **C. Cowan:** None. **A. Urban:** None. **B. Roska:** None.

**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 490.20/DP07/DD4 (Dynamic Poster)

**Topic:** D.07. Vision

**Support:** ERC Synergy Grant - ERC-2013-SyG

**Title:** Mapping of the cerebral structures involved in visual information processing with ultrafast functional ultrasound imaging in rodents

**Authors: *K. BLAIZE**[1], M. GESNIK[2], T. DEFFIEUX[2], J.-L. GENNISSON[2], J.-A. SAHEL[1], M. FINK[2], M. TANTER[2], S. PICAUD[1]
[1]Inst. De La Vision, PARIS, France; [2]Inst. Langevin, Paris, France

**Abstract:** The development of innovative therapies for vision restoration requires measuring visual cerebral activity with highest spatial and temporal frequencies as possible. A new functional imaging technique using ultrasounds for a fast acquisition of Cerebral Blood Volumes, which is a functional indicator of the neuronal activity, has been recently developed. Here we investigated whether we could use this new imaging technique to accurately map different visual areas as Visual Cortex (VC), Superior Colliculus (SC) and Lateral Geniculate Nucleus (LGN). We have mapped these structures after measuring the influences of flickering frequency and contrast on functional responses. We examined the responses of visual areas of anesthetized Long-Evans rats (n=8) to different visual stimuli. To do this, we first performed a craniotomy to expose the visual cortex of the animals so the ultrasound probe was approached at approximately 500 µm of the brain. Visual stimuli were flashed on a computer screen placed in front of the animals (~ 8 cm). Our visual stimulations consist in 5 repetitions of 30s visual stimulations followed by 30s of black screens. We have tested different visual parameters as flickering frequency, stimulus contrast or spatial frequency. Then, we compared the CBV recorded during visual stimulations to a baseline CBV. Using this technique, we could image with a high spatial resolution (~100µm x 100µm, FOV = 13 x 13mm²), and with an acquisition of 1 frame/s. The cerebral blood volume increased in a correlated fashion with the visual stimulation reaching up to 47% increase in SC (SEM: 1.8%), 46% in LGN (SEM: 1.6%) and 18% in VC (SEM: 2.4%) with correlation coefficients r=0.7 in SC, LGN and r=0.6 in VC. We also have demonstrated a lateralized activation of visual areas by flashing stimuli in one visual hemi- field. A retinotopy map has also been constructed. By shifting the ultrasound probe position by steps of 500 µm, we obtained 3D reconstruction functional maps of visual brain (VC, LGN and SC). Together, these results show that functional ultrasound imaging is an interesting technique to study the cerebral visual system. Spatial and temporal resolutions are high enough to discriminate and accurately monitor these structures - and substructures - involved in the

visual information processing. The anesthetic greatly disrupts brain activity, that's why it could be interesting to develop methods for awake animal's experiments.

**Disclosures: K. Blaize:** None. **M. Gesnik:** None. **T. Deffieux:** None. **J. Gennisson:** None. **J. Sahel:** None. **M. Fink:** None. **M. Tanter:** None. **S. Picaud:** None.

**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 490.21/DD5

**Topic:** D.07. Vision

**Support:** NIH NS064033

**Title:** Evaluation of functional connectivity in human visual system using invasive stimulation

**Authors: *A. SUGIURA**[1], Y. NAKAI[1], T. KAMBARA[1,3], H. MOTOI[1], E. ASANO[1,2]
[1]Dept. of Pediatrics, Children's Hosp. of Michigan, [2]Dept. of Neurology, Children's Hosp. of Michigan, Wayne State Univ., Detroit, MI; [3]Postdoctoral Fellowship for Res. Abroad, Japan Society for the Promotion of Sci. (JSPS), Chiyoda-ku, Tokyo, Japan

**Abstract:** We determined the spatial-temporal dynamics of neural propagation across lower- and higher-order visual systems, by intracranially measuring neural responses elicited by single-pulse stimulation. The present study included patients with focal epilepsy who underwent extraoperative electrocorticography (ECoG) recording as part of presurgical evaluation. The cortical surface was parcellated using FreeSurfer on individual MRI data. Trains of electrical stimuli were delivered to a contiguous pair of subdural electrodes at a frequency of 1 Hz for 40 seconds. Each electrical stimulus consisted of a square wave pulse of 0.3 ms duration, 5 mA intensity, and biphasic polarity. ECoG signals were averaged time-locked to the onset of each electrical stimulus; this analytic process yielded cortico-cortical evoked potentials (CCEPs) in electrode sites distant from the stimulated pair. In addition, time-frequency analysis was performed to determine the dynamics of stimulation-elicited neural modulations in given sites. Thereby, augmentation and attenuation of gamma (40-70 Hz) and high-gamma (70-110 Hz) activities were treated as summary measures of cortical activation and deactivation at given moments, respectively. We found that CCEPs generally consisted of an early negative wave (N1) followed by a late negative wave (N2). Stimulation of the lingual gyrus elicited CCEPs in the lateral occipital region. Stimulation of the lateral occipital region elicited CCEPs in the posterior-fusiform region, whereas that of the posterior-fusiform region elicited CCEPs in the lateral occipital and anterior-fusiform region. Time-frequency analysis revealed that brief gamma augmentation co-occurred with N1, whereas prolonged high-gamma attenuation co-occurred with N2. The present study provided unique evidence of feed-forward-preferential propagation

from the primary visual cortex to lateral occipital region as well as reciprocal propagation between the posterior fusiform and lateral occipital regions. The results of our time-frequency analysis support the notion that N1 component on CCEPs reflects an excitatory process while subsequent N2 reflecting an inhibitory one.

**Disclosures: A. Sugiura:** None. **Y. Nakai:** None. **T. Kambara:** None. **H. Motoi:** None. **E. Asano:** None.

**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 490.22/DD6

**Topic:** D.07. Vision

**Support:** Wellcome Trust/DBT India Alliance

DBT-IISc Partnership Programme

Tata Trusts Grant

**Title:** Local origins of electrocorticogram (ECoG) in visual cortex

**Authors: *A. DUBEY**, S. RAY
Ctr. For Neurosci., Indian Inst. of Sci., Bangalore, India

**Abstract:** Brain signals are recorded from humans and animals using a variety of electrodes of varying sizes. For example, local field potential (LFP) is obtained by low-pass filtering the raw signal obtained from a microelectrode (tip diameter of a few microns) inserted in the brain. Another signal is the electrocorticogram (ECoG), obtained by placing macroelectrodes (~2.3 mm diameter) on the exposed surface of cortex, which is widely used by neurosurgeons to identify the focus of seizure in epileptic patients. In this procedure, part of the brain (epileptic zone) that initiates the seizure is determined based on the distribution of epileptogenic activity on the ECoG electrodes, and is subsequently surgically removed. Therefore, it is critical to determine the cortical area that contributes to the ECoG (known as its 'spatial spread'), which is currently unknown.
To address this, we recorded brain signals from the primary visual cortex of three awake monkeys using both microlectrodes and ECoG electrodes. A small stimulus was flashed at different locations on the screen in a random order to estimate the visual spread for each recording site. Subsequently, the spatial spreads of ECoG and LFP (measured in micrometers) were estimated from the visual spread using a model proposed by Xing and colleagues (2009). The spatial spread of LFP was local (few hundred microns), consistent with some of the previous studies. Surprisingly, we found that the spatial spread of ECoG was on average only 3-4 times

greater than the LFP spread, suggesting that ECoG signal was also local, with a standard deviation approximately equal to the diameter of the electrode (~2.5 mm). Further, we compared the tuning characteristics of gamma oscillations in ECoG and LFP by presenting a full screen Grating stimulus. The tuning profiles of Gamma oscillations to orientation and spatial frequency in ECoG was comparable to LFP, further indicating that ECoG had a local origin. Our results justify the use of the usual grid spacing of 1 cm between ECoG electrodes commonly used in epilepsy surgeries, and in general the use of ECoG recordings from a particular brain area to infer local network properties of that area.
**References** Xing, D., Yeh, C.-I. & Shapley, R. M. Spatial Spread of the Local Field Potential and its Laminar Variation in Visual Cortex. *J. Neurosci.* **29,** 11540-11549 (2009).

**Disclosures: A. Dubey:** None. **S. Ray:** None.

**Poster**

**490. Visual System: New Tools and New Views**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 490.23/DD7

**Topic:** D.07. Vision

**Support:** 1539068

1430833

**Title:** Focal source localization of visual evoked potentials with tripolar electroencephalography in realistic head models Focal source localization of visual evoked potentials with tripolar electroencephalography in realistic head models

**Authors: C. TOOLE**[1], P. STEELE[3], R. BARTELS[3], J. DICECCO[2], *W. G. BESIO[2]
[1]Interdisciplinary Neurosci. Program, [2]Electrical Computer and Biomed. Engin. Dept., Univ. of Rhode Island, West Kingston, RI; [3]CREmedical Corp., East Greenwich, RI

**Abstract:** Knowing where sources of activity are in the brain can help 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 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 visually evoked potentials (VEPs). Subjects (n=5) were concurrently recorded with both EEG and tri-polar concentric ring electrodes (TCREs) during periods of checkerboard polarity reversal stimulus presentation. The stimulus was presented at 1.93 Hz for approximately 5 seconds followed by a 10 second pause. Said stimulus train was repeated for 5 minutes for a total of 3 times with a 60 second break between each, yielding a total of 600 trials. Due to hardware limitations, electrodes were placed on 16 of the standard 10-20 locations, excluding A1, A2, F7, F8, and T4. Surface potentials related to the visual stimulus 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 VEPs 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 VEP source signal.
[1] Besio et al "Tri-polar Concentric Ring Electrode Development for Laplacian" *IEEE TBME*. 2006.

**Disclosures: C. Toole:** None. **P. Steele:** None. **R. Bartels:** None. **J. DiCecco:** None. **W.G. Besio:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CREmedical Corp..

**Poster**

**491. Visual Pathways: To and From the Cortex**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 491.01/DD8

**Topic:** D.07. Vision

**Support:** EY001778

EY025422

P30-EY-008126

P30-HD-015052

**Title:** Cortical projections to the two retinotopic maps of primate pulvinar are distinct

**Authors: *B. MOORE**[1], A. BOAL[1], J. H. KAAS[2], C.-C. LIAO[3], J. MAVITY-HUDSON[4], V. CASAGRANDE[4]
[2]Psychology, [3]Dept. of Psychology, [1]Vanderbilt Univ., Nashville, TN; [4]Vanderbilt, Nashville, TN

**Abstract:** Our research has focused on the functions and anatomical organization of the primate visual pulvinar. Here we are interested in the specific roles that higher order nuclei of the pulvinar play in the visual system. Recent work has shown that there are two mirrored retinotopic maps in the pulvinar, one located dorsally and the other located ventrally. The presence of these two maps in the pulvinar raises important questions regarding the functional roles that this seemingly redundant nuclei might have. To examine the differences between cortico-thalamic projections to the two retinotopic maps of the pulvinar, we conducted a retrograde tracer study and examined labeled cortical cells.
Dual retinotopic maps of the pulvinar were distinguished electrophysiologically in two prosimian galagos (Otolemur garnettii) and were differentially labeled by pressure injections of either red or green fluorescently tagged cholera toxin subunit B (CTB) into each map. Special care was taken to ensure that each 4μL injection was made in locations that correspond retinotopically without allowing for overlap between the two injection sites. This was done to ensure that any double labeled cortical cells explicitly project to both of the pulvinar's retinotopic maps. After a 14-day survival period, the animals were perfused and cortex was sectioned coronally into 50μm sections. Tissue slides were imaged, cortical locations were determined via CO staining, and labeled neurons were localized and counted.
Results indicate that different populations of neurons in V1 and V2 project to the two pulvinar maps. Few, if any neurons were double labeled. Neurons within V1 and V2 were labeled by injections in either pulvinar map, but neurons in V1 were almost exclusively in layer 6, while neurons in V2 were in both layers 5 and 6. Furthermore, injections in the dorsal map labeled many more neurons in V2 than V1. These results support the view that the two pulvinar maps have different functions, and that neurons in V2 are important in driving the dorsal map. In monkeys, the dorsal map is located in the lateral pulvinar (PL) and the ventral map in the central lateral nucleus of the inferior pulvinar (PIcl).

**Disclosures: B. Moore:** None. **A. Boal:** None. **J.H. Kaas:** None. **C. Liao:** None. **J. Mavity-Hudson:** None. **V. Casagrande:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 491.02/DD9

**Topic:** D.07. Vision

**Support:** NEI 2R01EY017699

NIMH 2R01MH064043

**Title:** Causal role for the pulvinar in shaping cortico-cortical interactions

**Authors: *M. K. ERADATH**[1], M. A. PINSK[1], S. KASTNER[1,2]
[1]Princeton Neurosci. Inst., [2]Dept. of Psychology, Princeton Univ., Princeton, NJ

**Abstract:** The pulvinar is the largest nucleus in the primate thalamus and has topographically organized connections with multiple cortical areas, thereby forming extensive cortico-pulvino-cortical input-output loops. Neurophysiological studies have shown a role for the pulvinar in regulating information transmission within and between these cortical areas. However, the neural mechanisms underlying these cortico-pulvino-cortical interactions are not yet clear. Here, we explore the functional role of pulvinar in resting state connectivity between cortical areas V4 and LIP in macaques. We performed pharmacological manipulations by injecting muscimol ($GABA_A$ receptor agonist) and bicuculline ($GABA_A$ antagonist) into the pulvinar, immediately followed by simultaneous recordings from areas V4 and LIP, both in awake and anesthetized conditions. We used an MRI-guided approach for injectrode placement and further confirmed the extent of injection by visualizing Gadolinium MR contrast agent mixed with the pharmacological agent. Our preliminary results suggest that inactivating the pulvinar causally affects both V4 and LIP, possibly by similar neural mechanisms. The phase locking between lateral pulvinar and cortical areas was reduced in alpha frequencies following the muscimol injection. The alpha phase gamma amplitude coupling between V4 and LIP was decreased after the muscimol inactivation of the lateral pulvinar. These results further characterize the functional mechanisms with which the pulvinar regulates cortico-cortical interactions.

**Disclosures:** **M.K. Eradath:** None. **M.A. Pinsk:** None. **S. Kastner:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

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**Topic:** D.07. Vision

**Support:** NSF GRFP

NIH NEI R01EY017699

NIH NEI R21EY023565

PNI Innovation Award

**Title:** Effects of selective visual attention on macaque lateral, medial, and inferior pulvinar neurons

**Authors: *R. LY**[1], M. A. PINSK[1,2], S. KASTNER[1,2]
[1]Princeton Neurosci. Inst., [2]Dept. of Psychology, Princeton Univ., Princeton, NJ

**Abstract:** Recent studies suggest that the pulvinar nucleus of the thalamus plays an important role in visual attention. The pulvinar can be subdivided into lateral, inferior, and medial pulvinar. Firing rates in the lateral pulvinar increase with covert visual attention to a cued stimulus (Zhou et al., 2016) and to a cued location without a visual stimulus (Saalmann et al., 2012). Deactivation of the lateral pulvinar leads to attentional impairments (Petersen et al., 1987, Desimone et al., 1990). Whereas the lateral and inferior pulvinar are strongly connected with ventral visual stream areas, the medial pulvinar is strongly connected with higher order areas, including the frontoparietal attention network. If the medial, lateral, and inferior pulvinar are interconnected, attention signals from frontoparietal cortex could influence ventral stream areas through the pulvinar. Few studies have looked at the effects of attention on medial pulvinar neurons, and no studies have established whether the medial, lateral, and inferior pulvinar are interconnected.
We simultaneously recorded from tens of single units and multi-units in lateral, medial, and inferior pulvinar (15-30 per session) using linear microelectrode arrays in a macaque monkey while the animal performed a spatial attention task. We computed spatial receptive fields and attention indices for each unit and compared response properties of neurons in the three pulvinar subdivisions. Across the population, we computed cross-correlations of spiking activity as well as spike-field coherence to investigate functional connectivity within and between pulvinar subdivisions. In addition, using pairwise correlations between simultaneously recorded units, we developed a maximum entropy model to ask whether spiking of individual lateral and inferior pulvinar units can be predicted from the population activity of the pulvinar during different task states. These results extend the basic pulvinar mapping performed by Petersen et al. (1985) to demonstrate the population dynamics of the pulvinar during selective visual attention.

**Disclosures: R. Ly:** None. **M.A. Pinsk:** None. **S. Kastner:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 491.04/DD11

**Topic:** D.07. Vision

**Support:** CIHR

Becas Chile - CONICYT

**Title:** Pulvinar inactivation modifies the dynamics of visual cortical responses

**Authors: *N. CORTES**[1], B. OLIVEIRA FERREIRA DE SOUZA[1], C. F. CASANOVA[2]
[1]Ecole d'optometrie, Univ. De Montreal, Montreal, QC, Canada; [2]Univ. Montreal, Montreal, QC, Canada

**Abstract:** It is well known that the pulvinar establishes reciprocal connections with areas of the visual cortex, allowing the transfer of cortico-cortical signals through transthalamic pathways. However, the exact function of these signals in coordinating activity across the visual cortical hierarchy remains largely unknown. In anesthetized cats, we have explored whether pulvinar inactivation affects the dynamic of interactions between the primary visual cortex (a17) and area 21a, a higher visual cortical area, as well as between layers within each cortical area. We found that pulvinar inactivation modifies the local field potentials (LFPs) coherence between a17 and 21a during a visual stimulation. In addition, the Granger causality analysis showed that the functional connectivity changed across visual areas and between cortical layers during pulvinar inactivation, the effects being stronger in layers of the same area. We observed that the effects of pulvinar inactivation arise at two different epochs of the visual response, *i.e.* at the early and late components. The proportion of feedback and feedforward functional events was higher during the early and the late phases of the responses, respectively. We also found that pulvinar inactivation facilitates the feedback propagation of gamma oscillations from 21a to a17. This feedback transmission was predominant during the late response. At the temporal level, pulvinar inactivation also delayed the signals from a17 and 21a, depending on the source and the target of the cortical layer. Thus, the pulvinar can not only modify the functional connectivity between intra and inter cortical layers but may also control the temporal dynamics of neuronal activity across the visual cortical hierarchy.

**Disclosures: N. Cortes:** None. **B. Oliveira Ferreira de Souza:** None. **C.F. Casanova:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

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**Topic:** D.07. Vision

**Support:** RFBR grant 13-04-02170-a to S.S.

**Title:** Potentiation of the pulvinar leads to reorganization of direction preference maps in the cat visual cortex

**Authors: *S. I. SHUMIKHINA**, A. A. POTEKHINA, M. M. SVINOV
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**Abstract:** The lateral posterior-pulvinar complex (LP-Pulv) sends direct fibers to areas 17 and 18 in cats. It is shown that LP-Pulv can modulate cortical activity influencing response magnitudes, cortical gamma oscillations, synchronization between cortical neurons, and orientation selectivity. Here we hypothesize that LP-Pulv complex may also modulate such an important cortical property as its directional selectivity. Optical imaging of intrinsic signals was performed on the adult cat visual cortex. Monocular stimulation with moving square-wave gratings that changed continuously their orientation and direction was employed (method of Kalatsky and Stryker, 2003). Fourier decomposition was performed on the temporal signal to obtain orientation and direction maps. The phase and magnitude maps of the first harmonic were associated with directional components while such maps of the second harmonic were related to orientation components. After control direction maps were acquired, the high-frequency electrical stimulation of the LP-Pulv (200 Hz) was used for 10 s and post-tetanisation direction maps were recaptured. The degree of similarity between maps was measured on the pixel-by-pixel basis in the region of interest (ROI). It was observed that direction maps after the LP-Pulv tetanisation were markedly reorganized. Correlation coefficients between direction maps were strongly decreased to -0.1-0.2. Anisotropy in direction preference reversed or markedly increased. Computing orientation distribution histograms revealed large shifts in preferred orientation for each stimulus direction. Up to 68% of neuron populations acquired responses to opposite direction. The changes were not equally expressed for different orientations. The directional selectivity index also showed not equal changes for different orientations after LP-Pulv tetanisation. These preliminary results demonstrate that the LP-Pulv complex can modulate the directional selectivity of visual cortical neurons that can be important during attention processes.

**Disclosures: S.I. Shumikhina:** None. **A.A. Potekhina:** None. **M.M. Svinov:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 491.06/DD13

**Topic:** D.07. Vision

**Support:** CIHR Grant PJT-148959

**Title:** Modulation of the mouse primary visual cortex neuronal activity by the pulvinar

**Authors: *U. KEYSAN**, C. CASANOVA
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**Abstract:** Information about the visual world is processed by an ensemble of cortical visual areas, which follow a hierarchical organization. The primary visual cortex (V1) first receives most of this information through the lateral geniculate nucleus (LGN), before being conveyed to higher-order cortical areas. Aside from this connectional route, there is also a complex network of bilateral connections between areas of the visual cortex and the pulvinar, considered as the largest extrageniculate visual thalamic nucleus. Despite an increasing number of studies on pulvinar, the exact function of this thalamic complex remains unknown. In this study, we investigated the functional impact of the lateral posterior (LP) nucleus, the homologue of the primate pulvinar, on the activity of neurons in the primary visual cortex in mice using optogenetic stimulation. A channelrhodopsin-2 gene-carrying viral vector (AAV5.CaMKII.hChR2-eYFP.WPRE) was injected into the LP of wild-type (C57BL/6) mice. Extracellular recordings of the activity of V1 neurons were carried out using 16 and 32-channel silicon probes. The stimulation of LP was achieved with light pulses (470 nm, 20 pulse trains of 5 ms each at 10 Hz) delivered by a 4-channel optrode, which also recorded the thalamic activity. Visual stimuli consisted on drifting sinewave gratings of varying parameters (direction, contrast, spatial or temporal frequency and size). Our preliminary data shows that LP stimulation performed in conjunction with the visual stimulation decreases the amplitude of neuronal responses up to 50 %. To date, results indicate that this inhibitory effect is only observed in neurons in the infragranular layers. The response profiles of V1 neurons to size-increasing stimuli were also affected. These findings suggest that the pulvinar nucleus can exert layer-dependent contextual modulation on the activity of neurons in the mouse primary visual cortex.
Supp: CIHR.

**Disclosures:** **U. Keysan:** None. **C. Casanova:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

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**Program#/Poster#:** 491.07/DD14

**Topic:** D.07. Vision

**Title:** Functional and anatomical subdivisions of mouse visual thalamic area LP

**Authors: *C. BENNETT**, S. D. GALE, S. R. OLSEN
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**Abstract:** The lateral posterior nucleus of the thalamus (LP) is highly interconnected with all known regions of mouse visual cortex. Additionally, LP receives a dense projection from the superficial layers of the superior colliculus (SCs) and is thought to act as the main conduit through which information from the SCs reaches cortex. However, the role that LP plays in visual processing remains poorly understood, in part because previous studies have focused on

limited portions of LP. Here, we used high density silicon (Neuropixel) probes to conduct a broad survey of mouse LP visual responses, recording from >1000 units distributed throughout LP. By mapping these units to the Allen Institute's Common Coordinate Framework, we were able to register functional maps derived from our recordings to the anatomical projection maps in the Allen connectivity atlas. We found a striking correspondence between these functional and anatomical maps, supporting a coarse partitioning of LP into at least two subregions: a posterior SCs-recipient region (pLP) and an anterior non-SCs-recipient region (aLP). Neurons in these two zones differ in their visual response properties, and receptive field mapping reveals a clear reversal in elevation between aLP and pLP suggesting the existence of at least two retinotopic maps in LP. Properties of pLP neurons are similar to those of the SCs neurons that project to LP: large, horizontally-elongated receptive fields, strong surround suppression, spatiotemporal tuning for slow speeds, and stronger responses to object motion than to background motion. Conversely, aLP neurons have smaller receptive fields, weaker surround suppression, spatiotemporal tuning for high speeds, and stronger responses to full-field motion. Using these visual response properties alone we performed a clustering analysis on LP neurons and found two major functional clusters that segregate spatially into posterior and anterior populations. Thus, combined functional and anatomical evidence together point to the existence of multiple regions in LP that may support distinct visual processes.

**Disclosures:** **C. Bennett:** None. **S.D. Gale:** None. **S.R. Olsen:** None.

**Poster**

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**Title:** Interactions between population activity in cortex and striatum

**Authors: *A. J. PETERS**, N. A. STEINMETZ, K. D. HARRIS, M. CARANDINI
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**Abstract:** The striatum receives input from the entire cortex, and its outputs are routed both to other subcortical structures and back to the cortex. Corticostriatal connectivity has been shown to

be important for learning and decision-making, but the functional relationship between the cortex and striatum remains largely unknown.
To investigate this functional relationship, we combined widefield calcium imaging of the entire dorsal cortex with simultaneous high-density electrophysiological recordings in the striatum of awake mice. The use of 1 cm-long Neuropixels probes (ucl.ac.uk/Neuropixels) allowed us to record from a coronal trajectory spanning from the dorsomedial to dorsolateral edges of the striatum. Hundreds of units were sorted for each recording with Kilosort (Pachitariu et al, bioRxiv, 2016). We characterized the spatiotemporal patterns of cortical activity accompanying striatal firing using regularized linear regression.
Consistent with previously described corticostriatal connectivity, we found that cortical activity predicted striatal spiking in a topographic manner, such that dorsolateral striatum was most closely related to anterior cortex while dorsomedial striatum was related to progressively more posterior aspects of cortex. Spiking in the most medial band of the striatum was predicted by activity in the visual cortex. Moreover, responses in that band could be elicited by passively viewed visual stimuli. Large flickering gratings elicited the most reliable visual striatal responses, although receptive fields could sometimes be mapped also using sparse noise. Conversely, responses in more lateral regions of the striatum were neither elicited by visual stimuli nor predicted by visual cortical activity.
Corticostriatal topography and stimulus-driven responses were observed at both the multiunit and single-unit scale, but there was substantial heterogeneity in cortical fluorescence accompanying individual striatal units. Single units in the striatum could be parsed into cell types by waveform duration, firing rate, and inter-spike intervals, and included putative medium spiny neurons, tonically active neurons, fast spiking interneurons, and unknown interneurons. Preliminarily, there did not appear to be qualitative differences in the relationship between cortical activity and these different classes of cells.
These results confirm the functional relevance of corticostriatal anatomical projections and characterize the relationship between cortical and striatal activity at a mesoscopic scale.

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**Poster**

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**Topic:** D.07. Vision

**Support:** NIH Grant EY09593

**Title:** Visual response properties and receptive field structure in the thalamic reticular nucleus of the mouse

**Authors: *U. M. CIFTCIOGLU**[1], F. T. SOMMER[2], J. A. HIRSCH[1]
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**Abstract:** Before reaching cortex, retinal signals are processed by two separate inhibitory circuits in the visual thalamus. Local interneurons in the lateral geniculate nucleus (LGN) receive retinal input and provide feedforward inhibition to relay cells and each other. Gabaergic cells in the visual sector of the thalamic reticular nucleus (TRN) receive input from relay cells and project back to them in return to form the first feedback loop in the visual pathway. The TRN likely serves different roles, including bottom-up sensory processing and top-down control of spatial attention. To understand how the TRN influences relay cells and their targets in cortex, it is important to understand stimulus selectivity in the nucleus. While early studies suggested that reticular cells had limited sensitivity to stimulus shape, size or contrast, later work in cat and primate showed that reticular neurons are selective for complex visual features and that their receptive field sizes are comparable to those in the LGN, at a given eccentricity. The overall shape of receptive fields in the TRN is not altered by removing cortex and thus is likely sketched by geniculate afferents. However, the question of how these inputs are integrated with each other and influenced by connections among reticular cells is not understood and is experimentally difficult to explore in higher mammals. The mouse is a more tractable preparation and also offers advantages such as cell-type selective targeting through optogenetic means. Thus, we began to explore visual responses in the reticular neurons in anesthetized mice, using two experimental approaches. We made extracellular recordings to map receptive field structure, and used the (difficult) technique of whole-cell patch recording in vivo to study the underlying pattern of synaptic inputs. The receptive fields we mapped ranged widely in shape, from large (~50-60$^0$) and diffuse to smaller (~10-15$^0$) and structured, recalling the diversity recorded across the visual field in cat and monkey. There was also a wide range in spike-timing precision. Intracellular recordings revealed pronounced EPSCs, consistent with powerful afferent input, and pronounced hyperpolarizing currents, consistent with a strong influence of inhibitory connections. Taken together, our preliminary results suggest that the mouse may serve as a useful model to understand visual processing in the TRN.

**Disclosures: U.M. Ciftcioglu:** None. **F.T. Sommer:** None. **J.A. Hirsch:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

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**Topic:** D.07. Vision

**Support:** NIH grant EY022577

**Title:** Functional characterization of distinct cortical inputs to higher-order visual thalamus

**Authors: *M. A. KIRCHGESSNER**[1,2], E. M. CALLAWAY[1,2]
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**Abstract:** The lateral posterior nucleus of the thalamus (LP), which is the mouse analog of the primate pulvinar, is a higher-order visual thalamic nucleus that is thought to play an important role in visual attention. A key difference between LP/pulvinar and the first-order visual thalamic nucleus LGN is that LP/pulvinar receives two distinct cortical inputs: one from layer 6 that it shares with LGN, and one from layer 5 that avoids LGN. Prior studies of the morphological and physiological characteristics of these inputs have suggested that the two corticothalamic (CT) populations may have very different effects on activity in LP/pulvinar. In particular, it has been hypothesized that the layer 5 CT group, which has large synaptic terminals in LP/pulvinar that resemble retinal ganglion cell terminals in LGN, provide the primary "driving" input to LP/pulvinar and shape its visual response properties. Meanwhile, the layer 6 CT population, which has more numerous but smaller terminals in LP/pulvinar, may contribute "modulatory" input (e.g., Sherman 2016). However, whether layer 5 and layer 6 CT cells are functional drivers and modulators, respectively, of LP/pulvinar has never been directly tested. To answer this question, CT neurons in mouse V1 were selectively targeted for optogenetic manipulations using Ntsr1-Cre transgenic mice (layer 6) or wild-type mice with a retrograde virus encoding Cre injected into superior colliculus (layer 5). Multi-shank neural probes with high-density microelectrode arrays were used to record extracellular single-unit activity in LP of awake mice viewing drifting gratings while optogenetically manipulating the activity of either layer 5 or layer 6 CT neurons. This was used to determine each CT population's effect on visual and spontaneous firing rates and visual response characteristics in LP. The morphology and spatial distribution of each CT population's axon terminals relative to recording sites in LP was also examined. Preliminary results are consistent with the model of layer 5 and layer 6 CT neurons as functional drivers and modulators of LP, respectively, although they do not uniformly affect activity across the spatial extent of LP. For example, the effects of layer 6 CT activation can be facilitating or inhibitory depending on the recording location in LP. The results from this work not only address a longstanding question about the functional consequences of distinct cortical inputs to LP, but also provide the most complete characterization of visual response properties in the mouse LP to date. Overall, this work has implications for understanding LP/pulvinar's role in visual processing through its interactions with visual cortex.

**Disclosures: M.A. Kirchgessner:** None. **E.M. Callaway:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

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Research to Prevent Blindness/Lions Club International Foundation

**Title:** Differential volume loss of thalamic nuclei across aetiologies of cerebral visual impairment

**Authors: *L. MERABET**[1], E. BAILIN[2], C. M. BAUER[2]
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**Abstract:** Cortical/Cerebral Visual Impairment (CVI) is the leading cause of pediatric visual deficits in the developed world. It is often observed in children with early developmental brain damage, in particular those individuals born preterm who experienced a hypoxic-ischaemic event with resulting periventricular leukomalacia (PVL). Reduced neuronal number of the thalamus is often implicated in histology studies of PVL; however, it is not known whether MRI morphometry studies are sensitive enough to detect volume changes associated with PVL in specific thalamic nuclei. Thus, the current study examined volume of thalamic nuclei based on the Morel Histological Atlas.
A total of 7 individuals with CVI (Ages 14-24, mean 18.4 years, 4 PVL, 2 seizure, 1 neonatal infection) and normally-sighted and developed controls (Ages 15-24, mean 19.75 years) underwent a neuroimaging protocol on a 3T Philips Achieva system using an 8-channel phased array head coil. Two T1-weighted scans were acquired for each subject and analyzed in Freesurfer. Thalamic nuclei from the Morel MRI atlas (Krauth et al., 2010) were reverse transformed into each subject's anatomical space. Volume was calculated for each nucleus and assessed for CVI-related differences using t-tests and ANOVA in SAS.
Compared to controls, the CVI group showed an overall significant reduction in bilateral thalamus volume (CVI=4993.8 (1824.1); control=7607.7 (686.6), p = 0.02), which was likely driven by individuals with CVI due to PVL (PVL=3907.5 (813.9); non-PVL=7167.5 (689.4), p = 0.0087). Decreased volume in PVL compared to non-PVL causes of CVI were observed in the following thalamic nuclei: mediodorsal (PVL=101 (53); non-PVL=267 (181), p = 0.02), central lateral (PVL=654 (65); non-PVL=980 (613), p=0.015), paraventricular (PVL=4.2 (0.7); non-PVL=9.3 (3.2), p = 0.04), habenula (PVL=25 (9.1); non-PVL=74 (61), p=0.038), pulvinar (PVL=819 (387); non-PVL=1923 (1064), p = 0.013), medial geniculate (PVL=96.5 (24.6); non-PVL=240.5 (151), p = 0.016), lateral geniculate (PVL=92.7 (18); non-PVL=200.5 (92.6), p = 0.007), and ventral posterior (PVL=30 (4); non-PVL=86 (54), p = 0.009). All results are

presented as mean volume (sd) $mm^3$.
Overall, these results support the hypothesis that CVI is associated with reductions in specific thalamic nuclei, particularly those in the medial and posterior portions of the thalamus. Individuals with CVI due to PVL showed more widespread losses in thalamic nuclei compared to those without PVL. Thalamic damage in PVL may contribute to poor prognosis in children with CVI.

**Disclosures: L. Merabet:** None. **E. Bailin:** None. **C.M. Bauer:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

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**Topic:** D.07. Vision

**Support:** NSF 1421948

**Title:** Development of a visual pathway model to optimize sensory stimuli for brain-computer interface

**Authors: *C. TREMMEL**[1], F. SOBREIRA[1], S. H. WEINBERG[3], D. J. KRUSIENSKI[2]
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**Abstract:** Typical brain-computer-interfaces (BCIs) consist of devices to provide a sensory stimulus (e.g., video monitor, speakers, vibrotactors), an EEG measuring headset, and a computer processing unit for the decoding and feedback control. Common approaches such as the P300 Speller and steady-state visual evoked potential (SSVEP)-based interfaces use brain responses to visual stimuli to identify the user's intended target to achieve device control. BCI decoding algorithms have been researched for decades and have evolved to become more sophisticated. Rather than a continued focus on decoding algorithms, an alternative approach is to enhance brain response characteristics through the optimization of the stimulus patterns. This study aims to develop an extended model of the human visual pathway from the stimulus incident on the retina, through the lateral geniculate nucleus (LGN), to the electrode interface over the visual cortex. Information theoretic techniques will be used to create and test improved stimulus sequences based on the resulting visual pathway model. This model will leverage and combine existing work on modeling various components of the visual pathway and cortex. While models for some parts of the pathway such as phototransduction, single cortical neurons, and the electrode interface are already well-developed, the LGN and the visual cortex have a high complexity and only estimates about specific functions are possible. In order to create the best possible output, existing standalone models will be linked together by models of cortical

neurons. The more complex parts will consist of artificial neural networks (ANN) that will be trained with real-life data to match their function, with an emphasis on preserving physiological forms, connections, and positions. In preliminary experiments image sequences were presented to a virtual retina model that performs a spatio-temporal linear filtering, resulting in spike trains that are subsequently applied an ANN composed of three hidden layers with thirty hidden units each. The ANN is trained to simulate a 660 ms of an EEG response from a single channel over the visual cortex (i.e., Oz). The results show that this model successfully reproduces EEG responses to a simple contrast image stimulus at the input.

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**Poster**

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**Title:** A new human lateralized brain region: The primate pineal gland connects to v1 visual cortex and primary visual system

**Authors: *J. R. KORENBERG**[1], L. DAI[2], O. ABDULLAH[3], A. VANHOEK[3], M. C. BURBACK[4], M. SAUER[4], A. RAMIREZ[4], B. ZIMMERMAN[5], S. JOSHI[5]
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**Abstract:** The primate pineal in macaca fasicularis, is a bipartite structure (right left), each with dorsal and ventral regions seen at its posterior extent. Anterior projections of each part are highly topographic, extend primarily ipsilaterally but the more medial regions comprise both ipsilateral and crossing elements prior to exiting the gland. Clear multi - tract projections are seen to most components of the primary visual system as well as bilaterally to shared and distinct regions of V1/BA 17. Specifically, other regions include the optic chiasm and suprachiasmatic nucleus where both ipsi and crossed tracts continue in thin bands on the superior aspect of the optic nerves, likely to the retina. Projections also pass through the LGNs, bilaterally in distinct lateralized regions that connect in part in close association with the posterior inferior aspect of the optic chiasm. In humans, using the Connectome Lifespan pipeline acquisition sequences,

both left and right pineal elements project predominantly to the left hemisphere, similar to Zebrafish. These results provide a revolutionary view of human brain lateralization in a gland that regulates much of the limbic system and may provide a new origin and therapeutic targets for mental illnesses including autistic spectrum disorder and schizophrenia.

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**Poster**

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**Title:** Ultrastructural analysis of synaptic connectivity of local interneurons in the ferret visual thalamus

**Authors: *S. AHN**[1,2], V. SURESH[2], A. KUMAR[2], J. K. DAMRON[3], J. A. HIRSCH[1,2], M. E. BICKFORD[3]
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**Abstract:** The lateral geniculate nucleus (LGN) of the thalamus transforms the retinal signals it receives before sending visual information to cortex for further processing. The intrinsic circuits of the LGN comprise relay cells and local interneurons. Both types of cells share a similar, center-surround, receptive field structure but integrate synaptic inputs in different ways. Excitatory visual stimuli drive trains of unitary EPSCs in relay cells, but not in interneurons. Conversely, suppressive stimuli evoke serial IPSCs in interneurons but not in relay cells. Computational analyses suggest that these complementary patterns of response help to preserve information encoded in the fine timing of retinal spikes and to optimize the amount of information transmitted to cortex (ref Wang et al., 2011). While it is clear the trains of unitary EPSCs recorded from relay cells are produced by retinal afferents, the source of the serial IPSCs recorded from interneurons is not known. To reveal the potential synaptic circuits that underlie these distinct responses, we prepared ferret LGN tissue for ultrastructural analysis. Blocks of tissue including all layers of the LGN were cut into ultrathin sections, stained with an antibody against GABA tagged with gold particles, and imaged using an electron microscope.

GABAergic profiles were identified based on gold particle density. Both the dendrites and axons of interneurons form connections with neighboring cells. It is possible to distinguish synapses made by dendrites from those made by axons by the relative density of vesicles in the presynaptic element. Postsynaptic GABAergic elements were categorized as somata, dendritic shafts, or dendritic terminals. Retinal inputs were identified using the unique ultrastructural features of their mitochondria. Preliminary data (from 217 synapses) indicate that the large majority of presynaptic GABAergic profiles contact nonGABAergic profiles, presumed relay cells. Analysis of inputs to GABAergic profiles indicates that interneurons receive the majority of their input from two sources--retinal terminals and GABAergic terminals, including those from both dendrites and axons. This result suggests that synaptic coupling of interneurons generates the serial IPSCs that are recorded from interneurons during vision.

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**Poster**

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CNPq

**Title:** Anisotropic representation of orientation and direction selectivity in the visual wulst of owls

**Authors: C. SOUZA AMORIM**[1], P. VIEIRA[2], A. TURCHETTI MAIA[2], J. MACHADO DE SOUSA[2], C. GARCIA[1], L. LOPES BOREM PEIXOTO[2], K. E. SCHMIDT[3], S. NEUENSCHWANDER[4], *J. BARON[2]
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**Abstract:** Contour elements of static and dynamic visual stimuli are more accurately detected and discriminated when aligned with the horizontal and vertical axes than when obliquely oriented. This phenomenon, known as the "oblique effect", has been observed in a great variety of visual tasks and for animal species as diverse as goldfishes, octopuses, pigeons, cats and

monkeys. To date, the neural basis of this asymmetric processing of visual information remains elusive. In mammals, optical imaging and single-unit recording studies provided evidence for an overrepresentation of cardinal orientations in the early visual cortex, which suggests that the latter may mediate the oblique effect. With the aim of providing comparative insights into this issue, the present study seeks to determine whether such an overrepresentation is also present in the avian homologue of the primary visual cortex, namely the visual wulst. Previously, we and others have shown that most wulst neurons in owls are highly selective for the orientation and direction of simple stimuli like bars and sinusoidal gratings (Baron et al., 2007, *European Journal of Neuroscience*, 26 , 1950-1968). Here, we reassess this finding in a large dataset of isolated cells (n = 689) sampled from 11 awake burrowing owls (*Athene cunicularia*) and lightly sedated barn owls (*Tyto Alba*). Orientation/direction selectivity was quantified by a set of standard indexes, curve-fitting parameters and vector-based measures computed on neuronal responses to gratings drifting in 16 different directions (22.5 deg. increment steps) during 2000 ms. Our results reveal a clear heightened prevalence of neurons preferring near-horizontal orientations and downward motion in the visual wulst of both burrowing owls and barn owls. Unlike in area 17 of cats, this bias was not more pronounced for simple cells than for complex cells. Indicators of tuning precision tended to be more uniformly distributed in both orientation and direction spaces. The challenges for future research will be to understand the behavioral implications of these findings and the factors underlying the anisotropy of orientation and direction tuning preferences in the owl visual wulst.

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**Poster**

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**Title:** Figure-ground modulation in the human lateral geniculate nucleus

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**Abstract:** The lateral geniculate nucleus (LGN) is commonly portrayed as a passive way station between the retina and the visual cortex. However, growing research suggests that the human LGN is involved in more sophisticated visual and cognitive processes, showing modulation by covert attention (O'Connor et al., 2002) and evidence of orientation-selective processing (Ling et al. 2015). Here, we examined the role of the LGN in figure-ground processing, using high-resolution fMRI at 7 Tesla to record human brain activity. We investigated whether the LGN might show sensitivity to figure-ground organization in response to orientation-defined figures, as has been previously found in the early visual cortex. In two experiments, we asked 1) whether directed spatial attention is necessary for figure-ground modulation in the LGN, and 2) if feedback from cortical visual areas likely contributes to the enhancement of LGN responses to orientation-defined figures. We measured fMRI responses to orientation-defined figures presented to the left and right of fixation, cuing participants to spatially attend to one figure while ignoring the other. Spatial attention led to enhanced responses in the LGN, consistent with prior work, but more importantly, orientation-defined figures produced elevated responses even in the absence of attention. In a second experiment, we manipulated whether the figure and the surround stimuli were presented to the same eye or to different eyes. This design leverages the binocular organization of the early visual system: V1 is considered the first stage along the visual hierarchy in which signals from the two eyes are strongly integrated. Nevertheless, we found that the LGN was reliably modulated when figure and ground were presented to different eyes, implying that top-down feedback from binocular cortical neurons contributes to figure-ground modulation in the LGN.

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**Poster**

**491. Visual Pathways: To and From the Cortex**

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Eyesight Foundation of Alabama

**Title:** Photoreceptor-resolved receptive fields of parafoveal macaque LGN neurons

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**Abstract:** The receptive fields of neurons in the lateral geniculate nucleus (LGN) are primarily determined by signals arising from a small number of cone photoreceptors in the retina. For LGN neurons that represent visual space near the center of gaze, the number of cones serving the receptive field center can be quite small, ultimately thought to be just one cone for central foveal neurons, though this has not been directly measured. Ordinarily, optical constraints limit such measurements. A prior study that bypassed the optical limits using interference fringes found that parafoveal parvocellular neurons had field centers comprised of 2 or more cones (McMahon et al. 2001), suggesting a role for intraretinal circuitry in delimiting the fields. Adaptive optics can also be used to minimize optical constraints, and offers the advantage that the cones themselves can be targeted for stimulation. We used a multiwavelength adaptive optics scanning laser ophthalmoscope to simultaneously image the cone mosaic and present micron-scale movie stimuli for mapping LGN receptive fields in anesthetized macaques undergoing neuromuscular blockade. Imaging was performed with 840 nm light. Two stimulus channels were independently modulated to drive L and M cones equally (543 nm) or L cones preferentially (710 nm). In these green and red channels, binarized Gaussian noise movies were shown concurrently, at a spatial resolution of either 100 or 150 pixels/deg, with frames refreshing at 30 Hz, and using real-time retinally-stabilized delivery. Spatiotemporal receptive fields were constructed by reverse correlation of spike-triggered average (STA) movies. In 28 neurons recorded in 2 macaques, the noise movies yielded 22 receptive fields located between 0.4° and 4° from the foveal center. Receptive field center sizes were measured in the STA frame occurring 66 msec before the spike, based on stimulus pixels that had signals greater than 3 SDs of the noise in the STA frame 33 msec after the spike. For all cells at all eccentricities, field centers were less than half the diameter of those reported previously (Croner & Kaplan 1995; Levitt et al. 2001). In some cells, likely parvocellular, the field centers were of the same dimensions as the cone spacing measured at the site. Our data suggest that, with optical aberrations and eye motion minimized, the smallest parafoveal LGN receptive field centers may be revealed as being defined by inputs originating from one cone.

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**Title:** Lateral geniculate neurons in adult mice show robust ocular dominance plasticity

**Authors: *T. ROSE**, J. JÄPEL, S. WEILER, M. HÜBENER, T. BONHOEFFER
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**Abstract:** The change in ocular dominance (OD) after monocular deprivation (MD) is one of the most prominent models of experience-dependent plasticity in the neocortex. MD is known to evoke an OD shift in the binocular part of primary visual cortex (V1), but robust OD changes in the dorsolateral geniculate nucleus (dLGN) of the thalamus have not been reported so far. This led to the view that OD plasticity in the visual system is exclusively cortical in the mature brain. However, none of the recordings in dLGN to date have been performed chronically with single-cell resolution. Hence, changes in the eye-specific responsiveness of individual thalamic relay cells (TRCs) could have easily been missed. Furthermore, in contrast to the classical view of strict eye-specific segregation in dLGN, recent studies have reported that a fraction of TRCs integrates input from both eyes, which could provide a substrate for competitive TRC plasticity. This led us to re-evaluate thalamic binocularity and experience-dependent OD plasticity using chronic two-photon $Ca^{2+}$ imaging of TRCs projecting to binocular V1 of adult mice.
We conditionally expressed the genetically encoded $Ca^{2+}$ indicator GCaMP6m in the dLGN of Scnn1a-Tg3-Cre mice using adeno-associated virus and followed the visually evoked $Ca^{2+}$ signals of the same individual TRC axonal boutons in layer 1 (L1) of binocular V1 for up to 4 weeks before and after 6-8 days of contralateral eye MD. This provided a reliable and minimally-invasive longitudinal readout for the activity of TRCs in dLGN. We found that most (86%) dLGN cell boutons in L1 of binocular V1 were stably monocular during baseline. Following deprivation, however, more than half (55%) of the TRC boutons showed significant OD shifts, leading to population OD changes comparable in magnitude to those in cortical L2/3 neurons. Similar to cortex, TRC boutons that were exclusively responsive to the contralateral eye during baseline showed a prominent decrease in contralateral eye-evoked activity after MD. However, very different from cortex, initially monocular contralateral boutons also showed the most prominent increase in ipsilateral eye responsiveness. We are currently performing *in vivo* cortical silencing and *in vitro* optogenetic circuit mapping experiments to disentangle the contribution of feedback (i.e. corticothalamic) and feedforward (i.e. retinogeniculate) contributions to dLGN plasticity. Regardless of the mechanism, our results show that eye-specific responses in the

mature rodent dLGN can undergo substantial changes. We therefore conclude that purely cortical interpretations of OD plasticity need to be taken with a grain of salt.

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**Poster**

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**Title:** Different modes of visual integration in the lateral geniculate nucleus revealed by single-cell-initiated transsynaptic tracing

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**Abstract:** The thalamus receives sensory input from different circuits in the periphery. How these sensory channels are integrated at the level of single thalamic cells is not well understood. We performed targeted single cell-initiated transsynaptic tracing to label the retinal ganglion cells that provide input to individual principal cells in the mouse lateral geniculate nucleus (LGN). We identified three modes of sensory integration by single LGN cells. In the first, 1-5 ganglion cells of mostly the same type converged from one eye, indicating a relay mode. In the second, 6-36 ganglion cells of different types converged from one eye, revealing a combination

mode. In the third, up to 91 ganglion cells converged from both eyes, revealing a binocular combination mode in which functionally specialized ipsilateral inputs joined broadly distributed contralateral inputs. Thus the LGN employs at least three modes of visual input integration, each exhibiting different degrees of specialization.

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**Poster**

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**Topic:** D.07. Vision

**Title:** Fractal property and non-Gaussian dynamics of maintained spiking activity in parvocellular, magnocellular and koniocellular cells of marmoset lateral geniculate nucleus

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**Abstract:** Purpose: In absence of patterned visual stimuli, LGN neurons fire quite irregularly. We analyse the dynamics of spiking activity in LGN neurons for fractal properties and also compare these spiking dynamics with those described in cortical neurons. While, maintained activity in macaque retinal ganglion cells shows Poisson-like renewal statistics at sub-second timescales (Troy & Lee, 1994), at multi-second timescales, activity shows fractal (self-similar) characteristic in cat lateral geniculate nucleus (LGN) (Teich et al., 1997). Here we analyse the dynamics of spiking activity across long and short timescales in marmoset LGN neurons, specifically comparing parvocellular (P), magnocellular (M) and koniocellular (K) populations. We also show their diverse levels of coupling between local neuronal populations - ranging from highly correlated "choristers" to weakly correlated "soloists" (Okun et al, 2012), and a lognormal distribution of firing rates (Buzsaki, 2014).Method: Extracellular action potentials of visually-responsive cells were recorded in sufentanil-anaesthetised marmosets using a Neuronexus (16x2) silicon array probe. The visual stimulus was a uniform grey 20 deg. field, intensity ~50 cd/m2. The instantaneous firing rate, spike-triggered population rates (stPRs) and variability relative to Poisson process (Fano factor) over time windows between 0.1 s and 100 s were calculated.Results: The Fano factor of parvocellular (P, n =11/12), magnocellular (M, n=5) and koniocellular (K, n=26/29) neurons is close to unity for time windows less than 1 s (i.e. Poisson-like property) but rises monotonically with window width for time windows > 10 s (scale-free/Fractal property). Transition from Poisson-like to Fractal behaviour occurs at shorter time windows for K cells than for P and M cells ($p < 0.01$, Kruskal-Wallis test). Further, the distribution of firing rates of all LGN neurons follows a log-normal distribution and there was no

difference amongst neurons across stPR. Conclusion: Maintained firing activities of LGN neurons exhibits non-Gaussian dynamics, which are comparable to those described for cortical neurons (Churchland et al., 2010). This similarity suggests that thalamus contributes to cortical dynamics, and that to get a fundamental understanding of brain dynamics, an integrative investigation of thalamocortical interaction is required.

**Disclosures: B. Munn:** None.

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**Title:** Functional organization of retinal ganglion cell axons in the dLGN of awake mice

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**Abstract:** Relay neurons in the mouse lateral geniculate nucleus of the thalamus (dLGN) exhibit diverse and distinct visual tuning. Some mouse dLGN neurons can be sensitive to location, lights on, lights off, stimulus direction and/or orientation, while others are broadly suppressed by any stimulus contrast (Piscopo et al., 2013; Zhao et al., 2013; Suresh et al., 2016). Selective visual coding in relay neurons could result, in part, from specificity of retinal ganglion cell (RGC) input. Indeed, more than 30 functional types of RGC have been estimated in a recent imaging study in the mouse retina (Baden et al, 2016), providing a rich palette of visual feature tuning across RGC inputs to dLGN. How are different RGC axons organized in the dLGN and how do they converge to contribute to the selective tuning properties of the relay neurons? Technical limitations have prevented direct investigation of these important questions. Here we mapped the

functional organization of RGC axonal boutons with subcellular resolution in the dorsal region of mouse dLGN. By implanting a chronic cannula and cranial window above the dLGN, we could reliably record calcium events in hundreds of RGC axons and assess their visual tuning properties. With these preliminary data, we have begun to address several questions: how precise are retinotopic maps across RGC boutons in dLGN? Is there spatial organization to direction/orientation tuning? More specifically, do nearby boutons from different RGC axons show functional convergence that might give rise to specific receptive field properties in dLGN neurons?

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**Poster**

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**Title:** Temporal analysis of GABAergic effect on shaping the spatial frequency tuning of relay cells in the dorsal lateral geniculate nucleus of the cat

**Authors: A. KIMURA**[1,2], *S. SHIMEGI[1], F. UEDA[1], A. SATO[1], H. SATO[1]
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**Abstract:** The basic response properties of neurons in the lateral geniculate nucleus (LGN) are supposed to inherit from those of retinal ganglion cells. However, there is difference in spatial frequency (SF) tuning between LGN and retina, in which LGN neurons exhibit a band-pass type of tuning to SF, while the tuning of retinal cells is more low-pass. We recently found that intrageniculate GABAergic inhibition contributes to the transformation of SF tuning from retina to LGN (Kimura A et al., 2013). To understand how GABAergic inhibition elaborates the band-pass SF tuning property, we performed extracellular single-unit recording in the LGN of cats and examined the effects of blocking GABAergic inhibition on the SF tuning properties of visual responses by iontophoretical administration of gabazine, GABAA receptor antagonist, to neurons recorded. There are two sources of intrageniculate GABAergic inhibition, interneurons in LGN (feedforward inhibition) and perigeniculate nucleus (PGN) neurons (feedback inhibition). To obtain the clue of the sources of GABAergic inhibition, we focused on the temporal

characterisitcs of gabazine's action on SF tuning property and analyzed early (0-50ms) and late (50-100ms) responses separately. Administration of gabazine increased the visual responses of neurons, and changed the shape of SF tuning curve from band-pass to low-pass in both early and late responses. However, the effect of changing SF tuning curve was stronger in early than late response, suggesting that GABAgic inhibitory action via GABAA receptor is early and phasic. The detailed temporal analysis demonstrated that the inhibitory effect starts within 15ms after response onset. Therefore, the feedforward inhibition in LGN was thought to attribute to the inhibition because the feedback inhibition from the PGN takes more than 20 ms after LGN activation (Eysel, 1986). We conclude that GABAergic inhibition reshapes the SF tunings of early visual responses from LGN to retina via GABAA receptor, and the possible source of the inhibition is intrageniculate interneurons.

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**Poster**

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**Title:** The effects of stage II retinal waves on retinal ganglion cell projection to lateral hypothalamic area

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**Abstract:** The function of retinal ganglion cells (RGCs) can be divided into visual and non-visual function, mainly through their axon projection to thalamus and hypothalamus, respectively. Retinohypothalamic projection consists of medial retinohypothalamic tract (RHTm) and lateral retinohypothalamic tract (RHTl), the latter transferring environmental luminance to the lateral hypothalamus area (LHA), i.e, the retinorecipient region of the ventral zone of the rostral region of LHA (LHAavr). Previous studies showed that LHAavr mainly receives the inputs from the contralateral eye in adult rodent. However, it remains unknown whether this retinohypothalamic projection to LHAavr can be regulated during the developmental critical

period, when patterned spontaneous activity propagates through the developing visual system termed retinal waves. Particularly, stage II retinal waves (postnatal day P0-P9 in rodent) have shown critical for establishing the eye-specific segregation of the retinogeniculate projection. In this study, we determined the role of stage II retinal waves in pruning the retinohypothalamic projection to LHAavr. Stage II waves are generated by starburst amacrine cells spontaneously releasing acetylcholine (ACh) to the entire ganglion cell layer. Here, to block the stage II retinal waves, we injected the ACh receptor inhibitor (1 mM epibatidine in PBS) into binocular vitrea every 48 hr, starting from P1 to P9. Subsequently, the eyes were anterogradely labeled by CTB-488 and CTB-647 at P9 for 24 hr and the rats were scarified at P10 to examine the retinohypothalamic projection to LHAavr. Our results showed that the blockade of stage II retinal waves interferred the eye-specific segregation in the dorsal lateral geniculate nucleus (dLGN). By contrast, the LHAavr still received the main inputs from the contralateral eye, suggesting that stage II retinal waves may play a minor role in pruning the retinohypothalamic projection to LHAavr.

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**Poster**

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**Support:** NIH Grant EY013588

**Title:** Gain-control interactions in the lateral genicualte nucleus of the alert macaque monkey

**Authors: *D. ARCHER**, W. M. USREY
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**Abstract:** In the early visual system, nonlinear gain control mechanisms differentially modulate neuronal responses to visual stimuli. In the lateral geniculate nucleus (LGN) of primates, cell-class specific differences in the expression of nonlinear gain control are particularly apparent. Notably, contrast gain control is robust in magnocellular layers, where individual neurons show greater response gain at low stimulus contrasts and lower response gain at high stimulus contrasts. Two related manifestations of gain control, also reported to be most robust for magnocellular neurons, are extraclassical surround suppression and contrast-dependent phase advance (CDPA). Mechanisms that contribute to extraclassical suppression and CDPA in the primate LGN likely rely on multiple circuits including feedforward input from the retina, local thalamic inhibition, and feedback from the cortex. To gain insight into the circuits involved, we performed experiments aimed at identifying interactions between extraclassical suppression and

CDPA. Single-unit recordings were made from LGN neurons in the alert, fixating macaque monkey, and we measured responses to stationary and drifting sinusoidal gratings, varying in size and contrast, and centered over the receptive fields of recorded cells. Temporal profiles of responses evoked from suboptimal, optimal, and large size stimuli over a range of contrasts were compared. Consistent with the literature, response onset latencies advanced as stimulus contrast increased and as stimulus size increased from suboptimal to optimal size. We determined preferred response phase across stimulus size and across stimulus contrast, and CDPA (i.e., change in preferred phase across contrast for a given size) was compared across size to gain insight into the potential interaction between stimulus size and CDPA. While our results reveal a range of effects across our sample of cells, evidence for cell-class specific interactions were observed. CDPA was evident in most of the cells and contingent on stimulus size—observed more often and stronger when using suboptimal and optimal size stimuli than with large stimuli. Taken together, these results indicate differential interactions between the mechanisms that underlie extraclassical suppression and CDPA.

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**Title:** A model of multivalent distribution of bouton volumes reveals selective targeting of synaptic inputs on dendrite segments in lateral geniculate nucleus

**Authors: S. IMTIAZ**[1], E. N. KESKINÖZ[3], A. M. BAYA[2], C. LALA[3], E. E. MAHER[2], *A. ERISIR[2]
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**Abstract:** From Ray Guillery's electron microscopy characterization studies in the 1960s, to more recent complete circuit reconstruction analyses (Morgan et al., 2016), the synaptic circuitry in the visual thalamic nucleus, dLGN, has been one of the most intensely studied systems. Accumulated knowledge on its inputs, including from the retina, cortex, brainstem cholinergic neurons, inhibitory interneurons and thalamic reticulate nucleus (Erisir et al, 1997; Van Horn et al, 2000), where these inputs synapse (i.e., type of neuron; location on dendrite; in or outside of glomeruli), and the divergence/convergence of retinal fibers on geniculate targets, continue to reveal the structural basis for the dynamics of sensory information processing at the neuronal

level, and for maintaining the specificity of information flow in parallel pathways. Morphological characteristics of terminals seen with electron microscopy provide an invaluable tool in identifying origin-specific inputs without using track tracing or immunochemical approaches. This is particularly useful in utilizing serial EM imaging techniques, which enable accurate measurements of terminal volumes and other morphometric features. We have used SBEM stacks to develop a simple estimation tool that combined precision of 3D measurements and the reliability of unbiased sampling approaches. A multivarient analysis in R (mclust, mclustbootstrap) of terminal bouton volumes that make up randomly sampled dLGN terminals reveals five normally distributed subpopulations and confidence levels that represent five inputs (means varying $0.2\mu m^3$ to $15.4\mu m^3$). We have applied this analysis to identify the selectivity of different inputs on segments of relay and interneuron dendrites in the dLGN. We focused on axo-somatic inputs and several dendritic segments: appendage forming interneuron (F2) and relay dendrites, proximal and distal dendrites, and dendrite branching. Using *Reconstruct* software, we measured the volumes of terminal boutons that synapse on identified dendritic segments that were at least 30um in length. By comparing the volumes of terminals that were specific to each segment, to the subpopulations of the multivariate distribution, we determined the most probable origin of each bouton. We analyzed several features for each dendrite segment, including synapse density and clustering, terminal source, presence and complexity of glomeruli, and glial enclosure selectivity. We suggest this approach provides a less time- and resource-prohibitive alternative to complete circuitry reconstructions, while also yielding more specific information on the inputs that make up the geniculate circuitry.

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**Title:** Organization of the retinofugal pathway in the nine-banded armadillo (Dasypus novemcinctus)

**Authors: *B. E. SKINNER**, A. K. YORK, J. PADBERG
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**Abstract:** Previous research has shown that animals with forward facing eyes, such as predators and primates, exhibit partial crossing over of the retinofugal pathways at the optic chiasm. In

contrast, animals with laterally positioned eyes, such as rodents, exhibit almost exclusively crossed pathways; the retinal pathways terminate overwhelmingly on contralateral thalamic nuclei. The aim of the current study was to determine the organization of retinofugal pathways in the nine-banded armadillo (*Dasypus novemcinctus*), a member of the Xenarthra superorder and the only species of armadillo found in North America. Extant xenarthrans lack cone photoreceptors, and it has been suggested that stem xenarthrans became rod monochromats, in conjunction with a fossorial lifestyle. Based on their relatively lateral eye position, we predicted that the retinofugal pathways would exhibit nearly exclusively contralateral projection. Monocular injections consisting of twenty microliters of fluorescent anterograde tracer (.5-1% WGA+CTB Alexa-Fluor 555 with 2% DMSO) were placed into the vitreous humor of the eyes of armadillos. Cytoarchitectural stains such as Nissl and cytochrome oxidase (CO) histochemistry, along with immunocytochemical techniques using antibodies to calbindin, parvalbumin, and nonphosphorylated neurofilament protein, were used to identify the thalamic nuclei. The dorsal and ventral divisions of the lateral geniculate nucleus (LGN) stained intensely for CO, with a thin intrageniculate leaflet separating the two. Tracer label was observed contralaterally in both the dorsal and ventral divisions LGN and in the most superficial layer of the superior colliculus. An area within the dorsal portion of the contralateral LGN was void of label, which is indicative of the recipient zone of projections from the ipsilateral eye, as there was a corresponding patch of label on the ipsilateral side. This overall pattern resembles the organization found in marsupials and eutherian mammals with laterally placed eyes, and thus, it is likely that armadillo vision is predominantly monocular. Future functional studies are likely to reveal the extent to which a frontal binocular field, if any, is present in this species.

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**Title:** Neuronal pathway of direction selective ganglion cells in the mouse visual system

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**Abstract:** Direction selective ganglion cells (DSGC) enable vertebrates to perceive directions of moving objects. While cellular mechanisms of DSGCs have been extensively studied within the retina, downstream pathways of DSGCs have not been fully understood. It is believed that DSGCs form a distinct pathway, in parallel with X-cells, Y-cells, color coded ganglion cells, and melanopsin-containing ganglion cells. Genetic labeling and tracer injections revealed that DSGCs converge onto the shell of dorsal lateral geniculate nucleus (dLGN) before projecting to layer 1 of the primary visual cortex (V1), while X and Y neurons cluster in the core of dLGN before reaching layer 4 of V1. However, it is still unclear which layer of V1 cells receive the direction information first, since both layer 2/3 and layer 4 neurons stretch out their dendrites to layer 1 and both layers are comparably direction selective. We therefore hypothesize that both layer2/3 and layer 4 receive inputs from the shell of dLGN. We approach this problem with chronic in vivo two-photon microscope, chemogenetics and anterograde viral tools. Calcium traces from V1 layer 2/3 and layer 4 neurons are recorded while head-restrained awake mice run on a cylindrical treadmill, watching gratings waves moving at different directions through the contralateral eye. Silencing different parts of dLGN affects direction selectivity of layer2/3 cells in V1. Anterograde trans-synaptic tracers are injected into the shell and core dLGN respectively. Histological reconstruction shows that V1 layer 4 receives more input from shell dLGN than layer 2/3.

**Disclosures:** **J. Zhang:** None. **D.C.W. Chan:** None. **X. Wu:** None. **Y. Ke:** None. **W. Yung:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 491.28/DD35

**Topic:** D.07. Vision

**Support:** NIH: EY013588

NIH: EY012576

**Title:** Alpha (α) oscillations in the alert macaque lateral geniculate nucleus

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**Abstract:** Neural oscillations are hypothesized to play an active role in sensory processing as well as higher-order cognition. The most ubiquitous oscillations present in the mammalian brain are alpha (α) oscillations (8-14 Hz). Past studies using scalp EEG recordings over visual cortex report α-oscillations occur during periods of low-arousal and inattentiveness, and can influence performance on visual detection tasks. While the perceptual and behavioral states associated with α-oscillations have been extensively investigated, the underlying neural circuitry remains largely unknown. Previously, our laboratory demonstrated that corticothalamic feedback from primary visual cortex (V1) to the lateral geniculate nucleus (LGN) of the dorsal thalamus is strongly coherent in the α-band. Given that the LGN is the primary source of visual input to the cortex, receiving monosynaptic input from the retina and, in turn, projecting to V1, cortically driven α-oscillations could modulate retinogeniculate communication, determining in part which retinal spikes are transmitted through the LGN to visual cortex.
To investigate the influence of α-oscillations on visual processing in the geniculostriate pathway, we recorded from both the visual thalamus and V1 in three alert rhesus macaque monkeys using a combination of electrophysiological and viral driven, optogenetic techniques. As we have previously reported, α-oscillations are a robust feature of local field potentials (LFPs) in the LGN, while higher frequency band activity (e.g., gamma band) did not significantly differ from the "1/f" prediction. Contrary to the hypothesis that α-oscillations may strongly influence retinogeniculate communication, LGN neurons displayed little coherence with local α-oscillations and retinogeniculate spike efficacy was invariant to α-oscillation phase. Intriguingly, unlike α-oscillations recorded from scalp EEG, those present in LGN and V1 LFPs were present regardless of visual task engagement, were only weakly modulated by visual stimulation, and did not increase in amplitude when the eyes were closed. We propose that geniculostriate LFP α-oscillations are present during attentive visual processing and that the amplitude of α-oscillations is stable across a wide range of behavioral states. Ongoing studies are examining whether or not spatial coherence of α-oscillations changes with shifts in attention and/or behavioral state.

**Disclosures: H.J. Alitto:** None. **W. Usrey:** None.

**Poster**

**491. Visual Pathways: To and From the Cortex**

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NIH P30-EY003039

NIH R01-EY023591

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Eyesight Foundation of Alabama

**Title:** Wavelength-specific single cone responses in macaque LGN neurons

**Authors: *P. TELLERS**[1], L. C. SINCICH[2]
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**Abstract:** Color coding by neurons in the lateral geniculate nucleus (LGN) arises from the wavelength opponency signals created by intraretinal circuity, ultimately originating from cone photoreceptors with different spectral sensitivities. Using adaptive optics retinal microstimulation, we have previously shown that LGN neurons can be driven to fire action potentials with high probability when stimuli are as small as the size of a cone (Sincich et al., 2009). In that study, it was not possible to supply stimuli with different wavelengths, nor to determine if the variation in LGN responses from one cone to the next was due to variation in cone weighting. Thus, it was not clear if cone signals are all weighted the same, a feature that would impact color coding. Recent psychophysical evidence in humans suggests that single cones can have different weights (Bruce et al., 2015) and can signal wavelength-specific responses (Sabesan et al, 2016). Here we examine how LGN neurons respond to equivalent cone-targeted stimuli. We used a multiwavelength adaptive optics scanning laser ophthalmoscope to simultaneously image the cone mosaic and to deliver cone-sized stimuli to identified photoreceptors. Extracellular recordings from individual LGN neurons were made in anesthetized macaques undergoing neuromuscular blockade. Imaging was performed with 840 nm light, and two stimulus channels were used to deliver red (710 nm) or green (543 nm) stimuli, the latter wavelength selected to equally activate L and M cones. Transverse chromatic aberration correction was incorporated to allow stimuli to land on cones identified in the infrared movie images running at 30 Hz. Trials consisted of stimuli flashing at 3 Hz, with each flash randomly selected between the two wavelengths and from 5-7 intensities. Stimulus delivery was retinally stabilized in real time. In 5 neurons recorded in one macaque, receptive fields were located between 0.9° and 2.2° from the foveal center. Among groups of 4 cones tested for each neuron, we found that cones varied in functional weight by a factor of up to 3 for green stimuli that should drive L and M cones equally. This result agrees with cone weight differences found in retinal ganglion cells (Li et al., 2014). We also found differential responses to red stimuli, consistent with activity derived from M versus L cones. These preliminary data suggest that cone-targeted microstimulation may be used to resolve wavelength sensitivity at the photoreceptor level in vivo, once cone weighting is taken into account.

**Disclosures: P. Tellers:** None. **L.C. Sincich:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.01/EE1

**Topic:** D.07. Vision

**Support:** FWO

**Title:** Stimulus selectivity of macaque middle and anterior superior temporal sulcus body patches

**Authors:** *S. KUMAR[1], ***S. KUMAR**[1], I. D. POPIVANOV[2], R. VOGELS[1]
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**Abstract:** Monkey fMRI studies demonstrated two body selective patches in the Superior Temporal Sulcus (STS). One body patch, labeled MSB, is in the middle of the STS, close to face patches ML and MF, and was examined in a series of single unit studies (Popivanov et al., 2014, 2015, 2016). The anterior STS body patch, ASB, is close to face patch AL. Vogels and Kumar (SFN, 2016) observed a greater viewpoint-tolerant encoding of body posture and identity in ASB compared with MSB. That study employed only monkey bodies and did not examine ASB single units for other stimulus categories. Here, we recorded single unit spiking responses and local field potentials in ASB of the same 2 rhesus monkeys to the same stimulus categories as in our previous MSB studies (Popivanov et al., 2014): headless monkey bodies, headless human bodies, four-legged mammals, birds, H. Moore sculptures, monkey faces, human faces, fruits/vegetables and two sets of manmade objects (matching in aspect ratio to monkey and human bodies). As in MSB, the ASB LFP gamma power (30 -150 Hz) was greater for the body images (monkey bodies; human bodies; mammals; birds) compared to the other classes, including faces. The mean normalized firing rate was greater for bodies compared to non-bodies in ASB of each animal. The median Body Selectivity Index (BSI = [mean response to bodies - mean response to non-bodies] / [ |mean response to bodies| + |mean response to non-bodies|]) was similar in ASB (0.52; N = 159) and MSB (0.37; N= 214; Bayes Factor favoring null = 3.2). ASB neurons responded less selectively than MSB neurons to images of the same class: decoding (Linear Support Vector Machines (SVM)) of the individual exemplars of a stimulus class was significantly poorer in ASB compared with MSB, even when controlling for differences in Fano Factor between patches. Cluster analysis showed for MSB a body versus non-body clustering while a more heterogeneous clustering was present in ASB (e.g. human bodies distinct from monkey bodies). Linear SVM showed a significantly worse body versus non-body classification in ASB (84%) compared to MSB (92%). As in MSB, ASB neurons demonstrated size and position tolerance of their stimulus preference. A marked difference was the smaller degree of planar rotation selectivity of ASB compared with MSB neurons (Bayes Factor favoring

alternative > 10000). Surprisingly, given the more anterior location of ASB, the latency of the population responses and body category selectivity was similar in both patches. These data show that despite a similar overall body category selectivity at the single unit level, MSB and ASB differ in their stimulus selectivity, such as body orientation tuning.

**Disclosures:** **S. Kumar:** None. **I.D. Popivanov:** None. **R. Vogels:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

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**Topic:** D.07. Vision

**Support:** FWO G0A5613N

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IUAP 7/11

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HBP 604102 (EU H2020)

**Title:** Sub-millimeter resolution fMRI reveals human-like fine-scale organization of body regions in macaque monkeys

**Authors:** ***X. LI**[1], Q. ZHU[1], W. VANDUFFEL[1,2,3]
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**Abstract:** Previous monkey fMRI studies revealed two body-selective regions along the STS: the middle and anterior STS body complex (e.g. Pinsk et al. 2005, 2009; Popivanov et al. 2012). It is unclear, however, how they correspond to the human extrastriate (EBA) (Downing et al. 2001) and fusiform body areas (FBA) (Schwarzlose et al. 2005). Furthermore, high resolution imaging revealed that EBA consists of three separated compartments surrounding the MT cluster (Weiner and Grill-Spector 2011), but similar fine-grained structures have not yet been shown in macaques. Also, Lafer-Sousa and Conway (2013) showed interdigitating fMRI patches within IT cortex, selective for color, faces and places. It is unknown, however, how body patches are organized relative to other fMRI-defined patches at very fine scale. To address these questions, we studied the fine-scale organization of body regions in awake macaques using high resolution fMRI (0.6-0.7 mm isotropic voxels), and compared it with retinotopy, color, disparity and face activations at the same resolution in the same animals. To define body patches, we contrasted

monkey bodies with size-matched fruits, objects and monkey faces. To detect reliable activations, only reproducible regions across scan sessions were selected. Face patches were defined in the same way but with different contrasts (faces vs. fruits, objects and bodies). Color biased regions were localized using isoluminant color and achromatic radial gratings. A size-matched binocular disparity defined radial sine-wave grating and its monocular counterpart were used to activate disparity biased regions. Retinotopy was acquired using phase-encoded retinotopic fMRI mapping. Our results show multiple body activations surrounding retinotopically defined MT cluster in a crescent-like organization, surprisingly similar to the fine-grained organization of human EBA. Consistent body activations were found in V4d, V4t, PITd and rostral to MSTd, mostly corresponding to peripheral eccentricities as in humans. Similar face activations were found next to body activations corresponding to more foveal eccentricities. The latter form a crescent-like band around PITd body activations and were adjacent to the body patches. Several additional smaller body and face patches were found in anterior regions of IT and STS. Both body and face activations are largely separated from color and disparity activations, supporting parallel pathways in higher-level visual cortex. Together our results suggest that a surprisingly similar functional neuro-architecture exists in humans and monkeys for processing social relevant visual stimuli such as bodies.

**Disclosures:** **X. Li:** None. **Q. Zhu:** None. **W. Vanduffel:** None.

**Poster**

**492. Representation of Faces and Bodies**

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**Topic:** D.07. Vision

**Support:** NIH 2T32 EB008389

University of Minnesota CLA Brain Imaging Grant

**Title:** Cortical representation of body part relationships

**Authors: *A. BRATCH**, P. C. BURTON, S. A. ENGEL, D. J. KERSTEN
Psychology, Univ. of Minnesota, Minneapolis, MN

**Abstract:** Two regions critical for human body perception have been identified in human visual cortex: the extrastriate body area (EBA; Downing et al., 2001) and the fusiform body area (FBA; Peelen and Downing, 2005). While a wealth of evidence suggests that these areas process individual body parts and whole bodies, respectively, the regions' precise roles have yet to be elucidated. Here, we hypothesized that while neurons in the EBA represent individual body parts, neurons in the FBA also represent relationships, even at the level of pairwise connections,

between body parts. We tested this by measuring neural responses to body parts that were perceived as either forming a single, larger part, or as two disjoint parts. We used 3 Tesla fMRI (2.4 mm isotropic resolution, TE = 30.4 ms, TR = 2 s, multiband factor = 3) to measure neural activity in human subjects (N = 8). In an event-related paradigm, a hand and an elbow were presented within circular apertures on a gray background. The parts were presented either in their "normal" connected positions, or rotated within the apertures to induce the percept of an aligned arm or misaligned arm parts, respectively. Six rotations were used. We observed significantly higher activity in the FBA, but not the EBA, when subjects perceived the parts as aligned. When subjects did not actively judge alignment, and instead performed a task that demanded attention to individual parts, no difference between conditions was observed. Furthermore, a linear support-vector machine discriminated the pattern of activity for parts perceived as aligned vs misaligned at a level above chance in the FBA but not the EBA. These findings strongly suggest that the neural activity in the FBA underlies perception of relationships between body parts.

**Disclosures:** **A. Bratch:** None. **P.C. Burton:** None. **S.A. Engel:** None. **D.J. Kersten:** None.

**Poster**

**492. Representation of Faces and Bodies**

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**Topic:** D.07. Vision

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Hercules II Fonds

**Title:** Monkey brain fMRI responses to custom-designed animations of monkey hand- and tail-grasping actions

**Authors:** ***M. M. VISSERS**, S. SHARMA, P. A. FIAVE, S. KUMAR, K. NELISSEN
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**Abstract:** *Background*: Videos of human actions are widely used to study action recognition in humans and macaques. However, it is impractical to generate large, well-controlled batches of filmed videos to test various aspects of action recognition such as view invariance, generalization, coding of transitive versus intransitive actions, different effectors, action goals, etc. Moreover, creating such videos using monkey subjects to study conspecific action recognition is not straightforward.

*Methods*: We therefore designed (using open-source software Blender) an animated 3D monkey model performing various actions. Custom videos were created depicting a monkey grasping an object with its hand or tail. In addition, intransitive versions of these videos were made by removing the object from the animations. In order to validate these videos, fMRI brain responses were recorded in two macaques while they observed these animations in the scanner (Siemens 3T). Data were analyzed using SPM12 and Matlab.
*Results*: Consistent with previous monkey single cell (Caggiano et al., 2013; Kuravi et al., 2016) and fMRI (Nelissen et al., 2011) studies using videos of human actors, observing an animated monkey model performing transitive hand-grasping actions (compared to static controls), yielded significant activations throughout the action observation network, including extrastriate, STS, parietal, premotor and frontal regions. Interestingly, most of the regions responding to hand grasping observation (including those housing mirror neurons) also yielded significant responses for tail-grasping observation, as well as to intransitive hand or tail actions.
*Conclusion:* This study demonstrates the feasibility of using an animated 3D model to study brain responses to conspecific actions in monkeys. Our preliminary results suggest that typical motor regions containing grasping mirror neurons, also respond to observed motor actions that are outside the monkeys' own motor repertoire but share to same goal (grasping). The finding that even observation of intransitive actions yielded robust responses in these regions consistent with previous fMRI (Nelissen et al., 2005) and single cell data (Pani et al., 2014) suggesting that mere stimulus motion might be sufficient to drive at least a proportion of the neurons in these regions. More sensitive decoding and representational similarity analyses might shed light on the underlying organizational principle of these regions with respect to representing either immediate goals (Rizzolatti and Sinigaglia, 2016), causality (Caggiano et al., 2016) or the type of action effectors (Jastorff et al., 2010).

**Disclosures: M.M. Vissers:** None. **S. Sharma:** None. **P.A. Fiave:** None. **S. Kumar:** None. **K. Nelissen:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

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**Program#/Poster#:** 492.05/EE5

**Topic:** D.07. Vision

**Support:** NIMH Intramural Research Program

**Title:** Measuring neuronal selectivity for facial features in macaque inferotemporal cortex through adaptive sampling of feature space

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**Abstract:** For social animals like primates, faces are a behaviourally important class of visual objects, and they exhibit statistical variation across multiple dimensions. Previous studies have typically investigated the selectivity of single neurons in the inferotemporal (IT) cortex of macaques to variation of one or two facial features at a time, such as identity and head orientation. However, due to the high-dimensionality of the stimulus space and the time-constraints imposed by traditional recording methods, our understanding of how multiple facial features are encoded remains limited. To overcome these limitations and obtain a broader characterization of IT neuronal preferences for visual face features, we exploited two recent methodological advancements. First, we surgically implanted chronic microwire 'brush' electrodes, which allowed us to stably isolate single units over periods of weeks to months. The ability to record from the same neuron longitudinally increases the total number of visual stimuli that can be tested, thus improving coverage of stimulus space and characterization of the cell's selectivity across multiple stimulus dimensions. To leverage this, we developed an anatomically realistic three-dimensional virtual macaque avatar that offers continuous parametric control of over 50 variables (in addition to lighting, material and environmental varibles). To sample this high-dimensional feature space we used an adaptive approach whereby neuronal responses from one session were used to inform which regions of feature space to explore in the next session, with each generation of new stimuli being rendered offline using ray-tracing. Here we focused on a subset of possible variables that included head orientation, facial expression, identity, position in depth, depth profile, and virtual scale. We recorded from 128 channels in each of 3 macaque monkeys, targeting fMRI-localized IT 'face patches': ML, AF, and AM bilaterally. Monkeys viewed full-color 3D stimuli stereoscopically through a mirror haploscope, and maintained fixation while stimuli were presented. For most cells, firing rate was more strongly modulated by head orientation (azimuth and elevation angle) than by any other parameter tested, and this held true across all three face patches tested. However, a subset of cells showed highly specific selectivity for conjunctions of variables, such as head orientation and expression. The results demonstrate the value of adaptive sampling in a high-dimensional and parameterized feature space, thus improving characterization of the feature preferences of single neurons to complex stimuli.

**Disclosures: A.P. Murphy:** None. **D.A. Leopold:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.06/EE6

**Topic:** D.07. Vision

**Support:** NIMH IRP

**Title:** Norm-based encoding of faces in AF and AM face patches

**Authors: *K. W. KOYANO**[1], A. P. JONES[2,1], J. H. HONG[1], B. E. RUSS[1], D. A. LEOPOLD[1,3]
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**Abstract:** Face is a complex visual stimulus, and primates developed neuronal networks specialized for face recognition. In macaque monkeys, face-selective neurons were clustered in the inferotemporal cortices, constituting face patches that are mutually interconnected and process unique property of faces. Although a previous study showed that anterior inferotemporal neurons represent visual face stimuli by encoding difference from an average face (Leopold et al., 2006), it is still not clear whether the neurons in the face patches show this “norm-based” coding or not. Here we recorded single-units from two face patches located at the most anterodorsal (face patch AF) and anteroventral (AM) part of the inferotemporal cortices and examined their response tuning around an average face. The average face was created from 12 different identities of monkey faces by morphing technique. A series of stimuli was then computed based on the average face and each identity, producing “caricature faces” which has exaggerated features and “anti-faces” which has opposite features of the original identities. We recorded 30 face-selective AF neurons from three monkeys and 38 face-selective AM neurons from two other monkeys. Neurons from both face patches tended to respond weaker to the average face and respond stronger to caricature-/anti-faces, showing characteristic “v-shaped” tuning along the axis of anti-, average- and caricature-faces. Regression modeling of the response tuning showed that 76% of the face-selective neurons have the v-shaped tuning with its vertex around the average face. This tuning was not obvious in early transient response but became evident in later sustained responses starting 200 ms after stimulus onset. These results indicate a special role of the average face in both the AF and AM face patches, consistent with the concept of norm-based coding.

**Disclosures: K.W. Koyano:** None. **A.P. Jones:** None. **J.H. Hong:** None. **B.E. Russ:** None. **D.A. Leopold:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

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**Program#/Poster#:** 492.07/EE7

**Topic:** D.07. Vision

**Support:** NIMH IRP

**Title:** fMRI mapping of retinotopy using complex objects in rhesus monkeys

**Authors: *A. MESSINGER**, B. JUNG, C. SPONHEIM, L. G. UNGERLEIDER
Lab. of Brain and Cognition, NIMH, Bethesda, MD

**Abstract:** Visual processing in the primate brain occurs along two main pathways: a dorsal visual stream that primarily processes the spatial location of visual stimuli (the "where" stream) and a ventral visual stream that primarily processes the form and identity of those stimuli (the "what" stream). Using neurophysiology and fMRI, early visual areas have been shown to be retinotopically organized, with different portions of the cortex responding to different portions of the visual field. Such retinotopy is less apparent or absent in later stages of the ventral visual stream, where many neurons have receptive fields that span much of the visual field. Neurons in these ventral areas are selective for particular shapes, with neurons preferring the same visual category (e.g. faces or objects) clustering together. It is unclear how much, if any, spatial information is retained in these later stages of the ventral visual stream.
We measured fMRI responses in two rhesus macaques to the presentation of static monkey faces (and objects) in each of four quadrants of the visual field during a central fixation task. Stimuli were 7x7 degrees and were presented in a block design at an eccentricity of 6 degrees.
We evaluated responses in anatomically-defined areas throughout the visual stream using a standard anatomical template and coordinate system (Seidlitz et al., *Neuroimage*, 2017). As expected, responses throughout the visual system were almost always greater when the complex shape stimuli were presented in the contralateral quadrants than in the ipsilateral quadrants of the visual field. In early visual areas (V1-V4), regions responding more to the upper field quadrants were distinct from (and typically located ventral to) regions that responded more to the lower field quadrants.
In anterior ventral stream areas, contralateral stimuli generally elicited greater responses than ipsilateral stimuli and voxels responding significantly more to stimuli in the lower quadrants than the upper quadrants were more common than the reverse. This result indicates that some information about the position of visual stimuli is retained even in the later stages of the ventral stream, where complex shapes such as faces and objects are processed. The bias for lower-field stimuli suggests that face and object recognition may be more accurate or efficient in the lower relative to the upper visual field.

**Disclosures: A. Messinger:** None. **B. Jung:** None. **C. Sponheim:** None. **L.G. Ungerleider:** None.

**Poster**

**492. Representation of Faces and Bodies**

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**Topic:** D.07. Vision

**Support:** NIH RO1 EY 25670

NIH P30 EY 12196

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NIH S10RR021110

NIBIB P41EB015896

**Title:** Experience-dependent development of the visual system is anchored to an innate retinotopic organization

**Authors: *M. J. ARCARO**[1], P. F. SCHADE[2], M. S. LIVINGSTONE[3]
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**Abstract:** The adult primate visual system comprises a series of interconnected, topographically-organized areas arranged in two, dorsal and ventral, distributed hierarchies. This global organization, as well as the anatomical location and functional properties of individual areas throughout cortex, are similar across individuals, suggesting an early common program for the development of the visual system.
Here, we tracked the functional development of visual cortex over the first year of life in monkeys that were raised with normal or abnormal visual experience. We scanned monkeys using fMRI in a variety of visual tasks and under rest conditions starting as early as 8 days. To resolve the organization of visual cortex in infants, we characterized visual selectivity as well as patterns of functional connectivity (correlations).
Within the first two weeks of life, visual cortex was retinotopically organized in all monkeys regardless of visual experience. This organization preceded the emergence of other functional organization such as category-selective domains in inferotemporal (IT) cortex. When category-selective domains emerged, they were localized to retintopically-specific regions of visual cortex in each monkey. e.g., face domains developed within foveal regions of IT and scene regions developed within peripheral regions. However, visual experience shaped which domains developed. Specifically, monkeys raised without exposure to faces failed to develop face domains, but developed domains for other normally experienced categories such as hands and scenes. Functional connectivity patterns that overlapped with category domains emerged during early development in all monkeys. These connectivity patterns were localized to comparable

parts of IT across monkeys regardless of visual experience. However, category selectivity within these connectivity regions differed between monkeys based on visual experience, suggesting a dissociation between fMRI measured correlation patterns and underlying functional selectivity. Our results demonstrate a retinotopic organization present throughout the entire visual system, including IT, at birth. This organization is present even in monkeys raised with abnormal visual experience. Experience-dependent development is anchored to this retinotopic organization. Thus, despite substantial early organization, the primate visual system is immature at birth, and its organization is heavily modifiable through experience.

**Disclosures:** **M.J. Arcaro:** None. **P.F. Schade:** None. **M.S. Livingstone:** None.

**Poster**

**492. Representation of Faces and Bodies**

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**Topic:** D.07. Vision

**Support:** NIH Grant RO1 EY 25670

**Title:** The effects of early face deprivation on the macaque face-patch system

**Authors:** ***M. S. LIVINGSTONE**[1], M. J. ARCARO[2], P. F. SCHADE[2], J. L. VINCENT[2], C. R. PONCE[2]
[2]Neurobio., [1]Harvard Med. Sch., Boston, MA

**Abstract:** In humans and in monkeys, inferotemporal cortex is subdivided into domains that process different image categories, such as faces, bodies, or scenes. Here we asked whether experience is necessary for the development of category domains, specifically, the face patch system. We report that monkeys raised without exposure to faces did not develop face patches, but had normal domains for other categories, such as hands, bodies, and scenes. Furthermore, they showed normal retinotopic organization, indicating that their deficit was specific to the never-seen category. Therefore experience must be necessary for the formation of category domains. Our previous results had shown that intensive early experience can result in domains in monkeys for categories of objects that they normally never experience, indicating that experience is also sufficient for domain formation. Since face patches appear in foveally biased parts of IT, how monkeys view faces must be important in driving the stereotyped locations of face patches. Gaze tracking revealed that control monkeys looked preferentially at faces, even at ages prior to the emergence of face patches, but face-deprived monkeys did not. Thus selective early viewing behavior could bias category-specific visual responses towards particular retinotopic representations, thereby leading to domain formation in stereotyped locations in IT, without requiring category-specific templates or biases. We conclude that experience drives viewing

behavior, and viewing behavior precedes and sculpts domain formation. These results highlight the malleability of IT cortex early in life, and the importance of early experience on normal visual cortical development.

**Disclosures: M.S. Livingstone:** None. **M.J. Arcaro:** None. **P.F. Schade:** None. **J.L. Vincent:** None. **C.R. Ponce:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.10/EE10

**Topic:** D.07. Vision

**Support:** NIH grant RO1 EY25670

**Title:** Consequences of early face deprivation on viewing behavior in macaques

**Authors: *P. F. SCHADE**, M. S. LIVINGSTONE
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**Abstract:** Human and non-human primates tend to fixate on salient features and behaviorally relevant information in their visual environment. During free viewing, human and non-human primates preferentially look at faces, presumably due to the high amount of behaviorally relevant information that can be found in a face, such as its identity, emotion, and direction of gaze. It is debated, however, whether preferential face looking behavior is learned or innate. To address this, we asked if experience with faces is necessary for preferential face looking behavior. Using eye tracking, we monitored the gaze of normal and face-deprived macaques over the first year of life. Consistent with prior studies, our normal infant monkeys showed preferential face looking behavior. In contrast, we found that face-deprived monkeys did not preferentially fixate on faces during free viewing, indicating that preferential viewing of faces must be a learned behavior, and that faces must not be intrinsically interesting. Instead, the face-deprived monkeys looked more often at hands, when both faces and hands were presented, probably due to hands being more behaviorally relevant to them. We additionally monitored the gaze of the face-deprived macaques subsequent to the year-long deprivation period. Following the introduction of the face-deprived monkeys to social housing with other juveniles, there has been a shift in the viewing patterns, so that they now attend more to faces, yet they still show enhanced attention to hands, compared to normal juveniles. These data show that early experience, not an innate face bias, is the driving factor in how non-human primates, and likely humans, sample their environment.

**Disclosures: P.F. Schade:** None. **M.S. Livingstone:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.11/EE11

**Topic:** D.07. Vision

**Title:** Using electrical microstimulation to manipulate gaze following and face perception

**Authors: *I. CHONG**, H. RAMEZANPOUR, P. DICKE, P. THIER
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**Abstract:** Gaze following involves reading the eyes or head direction of an observed individual to identify possible objects of interest they are attending to and redirecting attention towards said objects. This is a process both humans and rhesus monkeys are capable of. We were able to circumscribe a “gaze following patch” (GFP) localized in the posterior superior temporal sulcus (pSTS) through human and monkey fMRI experiments, the latter followed by single unit neuronal recordings. That a highly specialized cortical area exists to extract directional facial information for redirecting the gaze of an observer highlights the importance of being able to follow gaze, yet it remains unknown what exactly the GFP is contributing to eye/head gaze following and to establishing joint and shared attention. Given the immense amount of socially relevant information we obtain from faces, one could imagine that the functional contribution of the GFP builds on information derived from various elements of the face processing network. The fact that one element of this face network, the middle face patch (mFP) lies in close proximity to the GFP (4-6mm) suggests a particularly important link. We used electrical microstimulation to perturb either the GFP or the mFP in the right hemisphere of two macaque monkeys trained in gaze following and identity matching tasks, and assessed subsequent effects on gaze following and face processing. In the gaze following task, the monkeys were presented with a portrait of one of four different monkey individuals, looking at one of four targets presented along a horizontal line. The monkeys were required to make a saccade towards the same target the portrait was looking at. In the identity matching task, the monkeys were required to direct saccades towards a spatial target unique to the identity of the monkey portraits they had been trained to associate. Here we report results from the first monkey as the experiments on the second one are still in progress. Our results indicate that the GFP and mFP are specifically relevant for gaze following and face processing respectively; stimulating the GFP led to impairments in gaze following whilst leaving identity matching intact, while targeting the mFP enhanced the ability of the monkey to match monkey identities without any significant effect on the ability to follow gaze. The evidence we provide here is a first step in establishing a causal role of the GFP in gaze following. The fact that stimulating the mFP did not disrupt gaze following does not necessarily contradict the assumed link between the mFP and the GFP;

possibly the latter may draw from redundant sources of face-related information and eventually also from the left mFP.

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**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.12/EE12

**Topic:** D.07. Vision

**Title:** The development and specialization of the visual system from infancy to adulthood

**Authors: *K. LESINGER**[1], G. ROSENTHAL[2], K. PIERCE[3], E. COURCHESNE[3], I. DINSTEIN[4], G. AVIDAN[5]
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**Abstract:** **Background:** Little is known about how the face perception network develops during early life. Here we investigated the development of this network from infancy to adulthood (1-35 y.o.; N=131) using an innovative method which registered anatomical and functional MRI scans of infants, children, adolescences and adults into a common space. This enabled us to use the regions identified as belonging to the face or place networks in adults for analyses in the other age groups in which such data were not available. Functional correlations across the identified ROIs were examined in resting state fMRI scans obtained in all age groups. **Results:** Functional connectivity was measured across ROIs belonging to the core face network (fusiform face area, occipital face area, superior temporal sulcus) and the place network (parahippocampal place area, inferior temporal sulcus, transverse occipital sulcus, inferior parietal sulcus). Interestingly, connectivity in the core face network was stronger in the right hemisphere across all age groups (infants, children, adolescences and adults). In contrast, the place network connectivity was stronger in the left hemisphere compared to the right hemisphere only in infants, while no difference was observed in the connectivity of this network between the right and left hemispheres in the other age groups. **Conclusions:** These findings reveal key details regarding the developmental trajectory of physiological changes unique to face representation. Specifically, the core-face network exhibited an early rightward lateralization from infancy, which is a well-known marker of the face processing system in adults.

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**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.13/EE13

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

**Support:** Canada Excellence Research Chair (CERC) in Cognitive Neuroimaging,

Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant (NSERC 418293DG-2012)

CIHR/NSERC Collaborative Health Research Project (CHRP 201110CPG)

**Title:** Don't represent what you cannot handle: Connectivity of category-specific regions in infants

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**Abstract:** In adults, the ventral visual stream contains category-specific regions that preferentially process faces, places and objects. The developmental origins of these regions were recently studied in infants using functional neuroimaging by Deen et al. (2017), who found regionally specific activation for faces and places, but not for objects. We aimed to characterise the development of these regions in a complementary way to Deen et al., by also characterizing the development of the broader networks that the category-specific regions participate in, using diffusion weighted images (DWI) (128 directions, 2 mm isotropic, no gap, b=0 mm $s^{-2}$) and applying diffusion tractography and machine learning. We used the parcellation of the ventral visual stream and fMRI localisers from the Human Connectome Project to identify the most face, place and tool selective regions, which were: the fusiform complex, the ventromedial visual area 2, and ventromedial visual area 3, respectively. We found that the face, place and tool regions could be localised through their unique signatures of connectivity. Using leave-one-subject-out cross-validation, three linear discriminant classifiers were trained to determine whether a voxel was inside or outside each of the three category-selective regions, from its strength of connectivity to regions across the rest of the brain. The classifiers' performance on identifying the regions was then tested on the left-out subject. All three regions could be robustly localised in adults ($p<0.001$). To test whether regions with similar category-specific signatures of connectivity were present in infants, we then acquired similar DWI data in infants between 1 and 9 months old (N=11, Mean Age=6.1 months) and performed tractography. The three classifiers trained on the full group of adults were then tested on each infant. We found that the classifiers

were able to localise all three regions in the infants ($p<0.01$). However, while the face and place regions were as strongly detected in infants as they were in adults (difference, $p>0.1$), the tool region was substantially more weakly detected (difference $p<0.01$). These results support Deen et al's findings that face and place specific activation is present in infants, but object specific systems are less developed, using a complementary neural measure. We further show that the broader networks of these category-specific regions are already connected in a way that is similar to adults. Our results are consistent with a broader framework that visual categories that are more passively perceived (faces and places) develop before those that are actively manipulated (objects).

**Disclosures: L.M. Cabral:** None. **L. Zubiaurre:** None. **C.J. Wild:** None. **A.C. Linke:** None. **R. Cusack:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.14/EE14

**Topic:** D.07. Vision

**Support:** Natural Sciences and Engineering Research Council of Canada

Connaught New Investigator Award

**Title:** Image reconstruction reveals the impact of aging and medial temporal lobe damage on face perception

**Authors: *C.-H. CHANG**[1], A. NESTOR[1], A. C. LEE[1,2]
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**Abstract:** A number of studies have demonstrated that face perception, as measured by performance accuracy on a variety of visual discrimination tasks, is impacted by healthy aging as well as by anterior medial temporal lobe (MTL) cortex damage. To date, however, there has been relatively limited insight into how precisely aging and MTL lesions affect the representations that underlie face processing, and how the subjective experience of face perception is altered. Here, we sought to address these issues by turning to a recent image reconstruction method that capitalizes on the structure of multidimensional face space. Neurologically healthy young participants, older adults and an amnesic patient with focal MTL damage first provided similarity judgments for pairs of face images presented simultaneously, with participant-specific ratings then used to construct a face space for each individual. Significant facial features and corresponding dimensions were subsequently derived from face space for every participant, and

then used to reconstruct the appearance of each face image that was presented. Our findings indicated that image reconstruction was successful for all groups of participants. However, reconstruction accuracy varied systematically across groups, with best results achieved for young adults. Converging with this, a hierarchical clustering analysis revealed differences in the representational space of the older participants and MTL patient when compared to the younger group. Our findings provide novel insight into age- and MTL lesion-related changes in face perception and demonstrate the utility of image reconstruction approaches to understanding face recognition across a variety of participant populations.

**Disclosures: C. Chang:** None. **A. Nestor:** None. **A.C. Lee:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.15/EE15

**Topic:** D.07. Vision

**Support:** ISF grant 296/15 to GA

**Title:** Behavioral mechanisms underlying visual expertise and their relation to face perception

**Authors: N. WEISS**[1], *G. AVIDAN[2]
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**Abstract: Background:** A major question in the face perception literature is whether faces comprise a distinct visual category that is processed by specialized cognitive mechanisms, or whether face processing merely represents an extreme case of visual expertise. A related question is whether objects of expertise are processed by the same cognitive mechanisms used for face perception. **Methods:** We address these issues by studying two groups of individuals with long-term visual expertise for either flowers or horses, naturally acquired due to personal interests and/or occupation. Using an eye-tracker, we conducted a gaze contingency experiment to examine whether these objects of expertise are processed holistically similarly to faces, as previously claimed in the literature. In this task, stimuli (flowers, horses and faces) are presented in three different conditions: 1. The whole stimulus is shown 2. An oval mask covers the visual field at the centre of the participant's gaze, concealing the local characteristics of the stimulus, and 3. An oval window is presented as a function of the participant's gaze, allowing only the presentation of local information. This behavioural task allowed fine-grained examination of the visual processes underlying perception of these stimuli, whether holistic or non-holistic. **Results**: Our findings revealed that experts did not necessarily use face processing mechanisms for objects of expertise. Specifically, a different perceptual process was used for each category of

expertise, as demonstrated by the different patterns of results obtained for each of these categories. **Conclusions**: The results imply that each visual category is processed as a function of its idiosyncratic characteristics. These findings shed new light on the seperability of the mechanisms mediating face processing compared to the processing of different categories of of visual epxertise.

**Disclosures: N. Weiss:** None. **G. Avidan:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.16/EE16

**Topic:** D.07. Vision

**Title:** Developmental prosopagnosics show reduced category-selectivity in right hemisphere areas selective for faces and other categories

**Authors: *J. GUO**[1], H. YANG[2], B. DUCHAINE[1]
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**Abstract:** Although many studies have investigated the neural basis of developmental prosopagnosia (DP), it remains unclear which face-selective areas are implicated in DP and whether their neural abnormalities extend to other category-selective areas. To address these issues, we scanned 22 DP participants and 27 controls with a dynamic localizer that effectively identifies posterior and anterior face-selective areas as well as areas selective for scenes, bodies, and objects. To avoid the complications inherent in comparing groups using typical ROI-based approaches, we analyzed each category-selective area by selecting a fixed percentage of the most selective voxels for each anatomical region that typically contains a category-selective response and then systematically probed the effect of ROI size on category-selectivity (Norman-Haignere et al., 2016). For faces, results showed significantly reduced face-selectivity in four face-selective areas in the right hemisphere (FFA, pSTS-FA, aSTS-FA, IFG-FA) along with weaker face-selectivity in OFA and ATL-FA. Face areas in the left hemisphere also tended to show weaker selectivity but only left FFA was significant. Results for other category-selective areas were mixed. DPs showed reduced selectivity in all three scene-selective areas in the right hemisphere (PPA, OPA, RSC), and weaker selectivity in left hemisphere areas but only the reduction in PPA was significant. For bodies, DPs showed reduced selectivity in right EBA and non-significant reductions in right FBA and left EBA. Object-selectivity in bilateral lateral occipital cortex (LO) was normal. In summary, our results show that posterior and anterior face-selective areas respond abnormally in DPs. The differences that reached significance were located primarily in the right hemisphere, which is consistent with the predominance of the right hemisphere in face perception. Reduced selectivity was also present in a number of areas

selective for non-face categories, and these reductions also tended be in the right hemisphere. Together, these findings suggest that many DPs have broad impairments across right hemisphere regions involved in visual recognition.

**Disclosures: J. Guo:** None. **H. Yang:** None. **B. Duchaine:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.17/EE17

**Topic:** G.03. Emotion

**Title:** Face perception: what we have learnt from face transplant patients

**Authors: *E. GÜLBETEKIN**[1], S. BAYRAKTAR[1], Ö. ÖZKAN[2], Ö. ÖZKAN[2]
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**Abstract:** The face is an important information source about its owner's gender, age, race and emotional state. Therefore, specific brain regions -fusiform face area, superior temporal sulcus- have evolved for face perception. Self-face recognition is also crucial to recognizing the bodily self and actively represented in the human cognitive and emotional system (Martini et al., 2015). Face transplantation has the potential to understand the link between self and other face perception. Due to long term facial somatosensory deprivation and thus having less feedback from his own face, face perception is thought to be altered in people having facial injuries since infancy. We observed that facial recognition memory performance was poorer in two facial transplant patients (Gülbetekin et al., 2017). Another phenomenon related to self-other face perception is enfacement illusion (EI): By touching the face of subjects who were viewing simultaneous touches on a partner's face, Bufalari et al.(2010) induced a novel illusion of personal identity called ''enfacement''. We tested two FTPs and compared their data with 21 healthy individuals for EI. The participants were asked to watch the video clips from a viewing distance of 150 cm. While watching the video, participants were touched on their face at the same locations as observed in the video in two conditions: synchronous, and asynchronous. The results indicated that the healthy subjects experienced stronger EI when the right side of the face was stimulated $X2\ (2, 28) = 17.64$, $p = .001$; however, the two FTPs did not show the right-sided bias for the illusion. Additionally, the EI was weaker in FTPs. The third issue on self-other face perception link is the influence of facial feedback on emotion recognition. In addition to visual and contextual routes to emotion recognition, people might also make use of sensorimotor simulation" (Wood, Magdalena Rychlowska, Korb & Niedenthal (2016). Some studies indicated that populations lacking facial expressions showed poorer performance in recognizing emotional expressions. FTPs have also difficulties in conveying emotional expressions. Therefore, we

tested the FTP's performance in "Reading the Mind in Eyes Test" if their difficulty in expressing emotions has any influence on decoding the emotional expressions of other faces. We found that their scores were lower than the mean score for their education level. Altogether we propose that long-term facial somatosensory deprivation may alter FTPs' ability to recognize faces and decode facial expressions, therefore intact facial feedback from one's own face seems to be required for precise facial processing.

**Disclosures: E. Gülbetekin:** None. **S. Bayraktar:** None. **Ö. Özkan:** None. **Ö. Özkan:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.18/EE18

**Topic:** D.07. Vision

**Support:** NSERC

**Title:** Face ensembles and identity processing: Decoding facial summary statistics from ERP signals

**Authors: *T. ROBERTS**, J. S. CANT, A. NESTOR
Univ. of Toronto Scarborough, Scarborough, ON, Canada

**Abstract:** Previous behavioural work has demonstrated our ability to extract summary statistics from groups of faces such as mean identity, emotion, and sex. However, despite the abundance of behavioural research, we know very little regarding the extraction of summary statistics for facial identity within the human visual cortex. Here, we used electroencephalography (EEG) to explore the neural basis of summary statistics for facial ensembles and its reliance on individual face representations. To this end, we collected EEG data while participants performed a one-back repetition detection task either with face ensembles (i.e., displays of 6 different faces presented simultaneously) or with single faces presented one at time. Critically, stimulus ensembles were designed so that, though they consisted of different individual faces, they could lead to the same summary representation, that is, the same average face. Pattern analyses were then conducted across spatiotemporal signals recorded across 12 bilateral occipitotemporal electrodes. These analyses showed that event-related potential (ERP) data support individual face classification and, also, point to the feasibility of ensemble classification. Importantly, these analyses serve to characterize the neural sensitivity to summary statistics beyond the processing of individual faces while, conversely, they also evaluate the relationship between ensembles and their individual elements. Further, they characterize the time course of face perception and confirm the informational value of spatiotemporal patterns in the proximity of the N170 ERP component. Thus, theoretically, the present investigation sheds new light on the neural basis of

ensemble processing in the context of face perception. Last, from a methodological standpoint, it serves to confirm the ability of EEG data to uncover the neural dynamics of ensemble perception.

**Disclosures: T. Roberts:** None. **J.S. Cant:** None. **A. Nestor:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 492.19/EE19

**Topic:** D.07. Vision

**Support:** NSERC

**Title:** Shape and surface-based facial image reconstruction: An evaluation of different neuroimaging modalities

**Authors: *D. NEMRODOV**, M. NIEMEIER, A. NESTOR
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**Abstract:** Neural-based reconstruction of image stimuli has been previously achieved with functional magnetic resonance imaging (fMRI) data as well as, more recently, with electroencephalography (EEG) data. However, a comparison of different modalities regarding their ability to support stimulus reconstruction along with their relative reliance on different classes of visual cues are yet to be explored. Here, we evaluate and compare the outcomes of facial image reconstruction based on fMRI, EEG and behavioral data. To this aim, we investigate the ability to reconstruct, from each modality, images of adult faces displaying different emotional expressions. Specifically, we aim to separately reconstruct face shape (i.e., a deformable configuration of fiducial points) and surface-based appearance (i.e., luminance and color properties of standardized 'shape-free' face morphs). Our results indicate that both shape and surface information can be recovered with above-chance accuracy from any of the modalities considered. However, surface is consistently retrieved with better accuracy than shape across all modalities. Interestingly, behavioral and fMRI-based reconstruction appear to perform equally well in terms of average accuracy, followed by their EEG counterpart. At the same time, EEG stands out by its ability to characterize the temporal dynamics of face encoding by supporting reconstruction for distinct time intervals. This investigation indicates that both shape and surface information can be recovered at multiple time points from the EEG signal and they are most effectively retrieved in the proximity of the N170 ERP component. Thus, our results speak to the feasibility and the relative success of stimulus reconstruction based on different data types while, theoretically, they shed light on the visual mechanisms for face recognition and their neural dynamics.

**Disclosures:** **D. Nemrodov:** None. **M. Niemeier:** None. **A. Nestor:** None.

**Poster**

**492. Representation of Faces and Bodies**

**Location:** Halls A-C

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**Topic:** D.07. Vision

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**Title:** Smaller, slower, and shorter-lived: Context-dependent temporal characteristics of visual adaptation in human ventral temporal cortex

**Authors: *V. RANGARAJAN**[1], K. S. WEINER[2], C. JACQUES[4], J. PARVIZI[3], R. T. KNIGHT[5], K. GRILL-SPECTOR[2]
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**Abstract:** Repeated presentations of visual stimuli produce decreased neural responses within human ventral temporal cortex (VTC) - a phenomenon known as repetition suppression or adaptation. Several neural mechanisms, including scaling, sharpening, and facilitation, have been proposed to explain this phenomenon. Different than scaling and sharpening, facilitation proposes that neural responses are comparable in amplitude, faster to peak, and shorter in duration for repeated than nonrepeated stimuli. To distinguish between proposed mechanisms of adaptation, we tested the dynamics of responses to repeated stimuli utilizing the high spatial and temporal resolution of electrocorticography (ECoG) from 6 subjects (2 female) implanted with intracranial electrodes over the right (n=4) and left (n=2) VTC. Subjects were presented with images of houses, bodies, cars and faces. We first identified which electrodes were face-selective in each subject. Then, using independent data, we quantified the functional dynamics of responses to repeated images presented either after intervening stimuli (experiment 1) or immediately (experiment 2).
We found a concentration of face-selective electrodes (n=43) in the lateral fusiform gyrus and inferior temporal gyrus. Many of these electrodes (54%) exhibited significantly reduced high frequency broadband (HFB: 70-150 Hz) power to immediate repetitions of faces. Contrary to predictions of the facilitation model, responses to immediate repetitions of a face were slower ($p<0.004$), smaller ($p<10^{-5}$), and shorter-lived than responses to the first presentation (area under

the curve for 1st vs 2nd presentation, $p<10^{-8}$, KS-test=0.6744). For repetitions with intervening stimuli, we also found reduced responses to repeated vs. first presentations, although less attenuation than for immediate repetitions. However, there were no significant changes to the onset ($p>0.05$) or duration (area under the curve, $p=0.057$, KS-test=0.2791). Together, these findings provide evidence that mechanisms other than facilitation likely underlie processing of repeated stimuli in human VTC and immediate and interleaved repetitions may involve different neural mechanisms. As adaptation is prevalent across the brain, these data have important implications for understanding neural mechanisms of repetition effects.

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**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 493.01/EE21

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** JHUAPL GRANT 1126412

**Title:** An objective classifier of expertise in united state marine corps combat aviators

**Authors: A. M. NOZIMA**[1], *S. MARTINEZ-CONDE[2], J. I. CASTRO[1], L. L. DI STASI[3], *S. MARTINEZ-CONDE[2], M. B. MCCAMY[5], E. GAYLES[6], A. G. COLE[7], M. J. FOSTER[7], B. HOARE[7], F. TENORE[8], M. S. JESSEE[9], E. POHLMEYER[10], M. CHEVILLET[9], A. CATENA[4], W. C. DE SOUZA[11], G. A. JANCZURA[11], S. L. MACKNIK[12]
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**Abstract:** We and others have previously shown that oculomotor dynamics serve as a valid biomarker for fatigue and high mental workload, and other brain states—measured in applied environments. We obtained eye movements from both instructor and trainee United States Marine Corps (USMC) combat aviators to determine the differences in dynamics as a function of expertise. The pilots flew different simulated mission types and we determined their ocular kinematics—as a function of mission type and cohort—across many dimensions. We observed

that there are differences in specific eye movement signals between novice and expert helicopter pilots. From this data we created a classifier of expertise, which performed with an accuracy of >70%. We then studied whether novice pilots benefit more from viewing movies of experts performing emergency procedures or the same movies with the expert's eye position scanpaths overlaid. As an innovation, we did not measure the benefit to novices as a function of performance, but instead measured their oculomotor dynamics as a function of the expert scanpaths—assessed by our objective expertise discriminator. We tasked novice pilots with repeatedly resolving an Emergency Procedure (dual engine failure cascade), followed by watching a video with the expert eye position indicated, and the other half watched the video without the eye movements superimposed. Pilots who were given access to the expert's scanpaths significantly changed, in comparison to pilots who saw the same movies without scanpaths. These results suggest that physiological biomarkers such as oculomotor dynamics may provide a rich source of data—in a short amount of time and within challenging operational environments. This also suggests that our oculomotor systems learn to use eye tracking information—even without being instructed to—very quickly. Future research will determine if the fast oculomotor learning we observed translates to true improvements of performance.

**Disclosures:** **A.M. Nozima:** None. **S. Martinez-Conde:** None. **J.I. Castro:** None. **L.L. Di Stasi:** None. **S. Martinez-Conde:** None. **M.B. McCamy:** None. **E. Gayles:** None. **A.G. Cole:** None. **M.J. Foster:** None. **B. Hoare:** None. **F. Tenore:** None. **M.S. Jessee:** None. **E. Pohlmeyer:** None. **M. Chevillet:** None. **A. Catena:** None. **W.C. De Souza:** None. **G.A. Janczura:** None. **S.L. Macknik:** None.

**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 493.02/EE22

**Topic:** D.09. Visual Sensory-motor Processing

**Title:** Anti-saccade < visual search performance in schizophrenia

**Authors:** *W. C. SENA[1], ***W. C. SENA**[1], *W. C. SENA[2], L. GONÇALVES[1,3], L. GENARO[1], L. SCORIELS[1], A. GUIMARÃES[3], F. BRAGA[4], R. PANIZZUTTI[1,2]
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**Abstract:** Sensory deficits and cognitive impairments contribute to poor psychosocial functioning in patients with schizophrenia. These patients use inefficient visual search strategies and show reduced ability to make correct anti-saccades. Impairments related to the visual system can be quantified using psychophysical parameters of visually guided eye movements. This study aimed to verify the importance of higher versus lower order visual information processing

in schizophrenia patients and its relationship to specific cognitive domains. Therefore, we compared the performance of schizophrenia patients and healthy controls while executing two oculomotor tasks. The visual search task requires finding a vertical gabor target among several horizontal distractors with the same contrast (efficient search) and vertical distractors with a higher contrast compared to the target (inefficient search). The anti-saccade task requires looking to the direction (pro-saccade) or the opposite direction (anti-saccade) of a luminescent stimulus. Moreover, we performed correlations between the visual processing outcome measures and specific cognitive domains scores in the patients group. Patients made significantly more fixations to find the target in the visual search task (efficient search: t=2.16, p=0.04; inefficient: t=3.37, p=0.003) and showed elevated error rates for the anti-saccade task (pro-saccade: t=2.25, p=0.04; anti-saccade: t=2.11, p=0.05) compared to controls. The patients group showed a correlation between the inefficient search and spatial memory and learning scores (r=-0.64, p=0.04) and between anti-saccade error rates and verbal memory and learning scores (r=-0.85, p=0.001). These results confirm that patients with schizophrenia have deficits in visual search and anti-saccade neurobiological correlated processes, which may be associated to memory and learning cognitive domains. To remediate these impairments, we are currently testing the efficiency of a neuroplasticity-based cognitive training.

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**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 493.03/EE23

**Topic:** D.09. Visual Sensory-motor Processing

**Title:** Neural correlates of presaccadic compression: An ERP study

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**Abstract:** The perceptual consistency viewed across the large quantity of saccades made has been posited to be the result of a visual mechanism known as presaccadic visual remapping which updates visual representations prior to the execution of a saccadic eye movement. A byproduct of remapping is the occurrence of a significant spatial distortion prior to a saccade (known as presaccadic compression) in which there is a systematic mislocalization of targets toward the spatial location of a planned saccade. Several studies have illustrated such mislocalization, demonstrating that observers systematically report stimuli to appear spatially shifted toward a saccade target. Single-cell recordings in monkeys have demonstrated rapid alteration to receptive field dynamics in posterior parietal cortex and retinotopically organized

extrastriate visual cortices that are consistent with a remapping of visual space in anticipation of an impending saccade. Here, we use event-related potentials (ERPs) to examine the link between presaccadic neural activity and the percept of presaccadic compression in the human visual system. Observers performed a cued saccade task, requiring them to make leftward or rightward saccades when cued by an auditory tone. On 85% of trials, a probe stimulus (vertical line) briefly flashed at a pseudorandom delay following the saccade cue. After completion of the saccade, observers then used the mouse to indicate the perceived position of this probe. On the remaining 15% of trials, no probe stimulus was presented and observers simply made a saccade to the target location. These 'saccade only' trials were used to remove electro-ocular eye movement artifacts from probe trials. Trials were binned into three bins according to the relative timing of probe onset to saccade onset (-225 to -151 ms, -150 to -76 ms, and -75 to -1 ms). ERPs and mislocalization effects were calculated within each of these time windows. Preliminary results demonstrate a standard presaccadic mislocalization effect in the -75 to -1 ms time window leading up to the saccade and further indicate the occurrence of a potentiated visual N1 component of the visual evoked potential within this same time window. This reveals a potential correlate of presaccadic compression in human extrastriate visual cortex, and is consistent with single-cell work in monkeys.

**Disclosures:** **A. Rodriguez:** None. **S.M. Long:** None. **M.A. Gannon:** None. **N.A. Parks:** None.

**Poster**

**493. Eye Movements and Perception**

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**Program#/Poster#:** 493.04/EE24

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NIH Grant 5T32 EY017271-08

NIH Grant EY022928

**Title:** Population interactions between prefrontal and visual cortex during eye movement planning

**Authors: *M. A. SMITH**, S. B. KHANNA
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**Abstract:** During active vision, prefrontal regions of cortex that encode eye movement plans and are important in working memory interact continuously with visual cortex where the scene is parsed and salient information is identified. Anatomical studies have demonstrated connections between these regions of cortex, and some electrophysiological investigations have identified

functional interactions. However, very little is known about the way in which signals in these two regions interact at the population level. The spatial structure of these interactions is particularly important in active vision, where attention and eye movements can be directed rapidly across the visual landscape. One means of studying the language of this communication is through the correlated variability among pairs of neurons, a signature of functional interactions among neurons. It has been suggested that changes in correlated variability impact the ability of a given neural population to encode information, such as a visual stimulus. It is unclear, however, how correlated variability propagates across cortical regions and across large areas of visual space contingent on an eye movement plan. Visual cortical area V4, an intermediate level along the visual processing pathway, and dorsolateral prefrontal cortex (PFC), an area that represents working memory and eye movement signals in its delay period activity, both factor in the transition from visual stimulus to eye movement. We used two 96-channel “Utah Arrays” to record from groups of V4 and PFC neurons simultaneously in alert rhesus macaque monkeys performing a conventional memory guided saccade task. We measured the spike count correlation (also known as noise correlation) between pairs of simultaneously recorded neurons, both within and between V4 and PFC, during the delay period before the eye movement was made but after the visual stimulus had been presented. Correlations in V4 and PFC decayed with increasing spatial distance between recorded neurons, as observed previously in numerous cortical regions. Correlation between PFC and V4 neurons varied depending on the spatial relationship between the PFC and V4 receptive fields. Furthermore, PFC neurons with ipsilateral and contralateral receptive fields displayed distinct functional interactions with V4. These functional signatures may reflect the role of PFC in integrating and representing information about memory and motor planning across the entire visual field.

**Disclosures:** **M.A. Smith:** None. **S.B. Khanna:** None.

**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

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**Program#/Poster#:** 493.05/EE25

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** IBS-R015-D1

**Title:** The interaction between Bayesian prior and attention in visually guided eye movements

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**Abstract:** When we interact with the environment and make appropriate behavioral responses, our brain relies not only on the incoming sensory information but also on a prior knowledge based on recent experience. The influence of the prior knowledge becomes more prominent when the sensory evidence is weak or ambiguous. Because attention is a cognitive factor that is known to boost the gain of sensory representation, it is possible that attention interacts with the Bayesian prior and affects behavioral responses. To understand how attention interacts with the Bayesian prior to influence sensory-motor behavior, we asked human subjects to perform a smooth pursuit eye movement task while we controlled the strength of sensory motion and attention independently under the same prior condition. The pursuit target was a random dot patch whose speed was fixed at 16 deg/s, while the direction was randomly selected from three motion directions (pre-determined prior direction, ±30 deg). We controlled the strength of visual motion by randomly varying luminance contrast of the pursuit target (100% or 12%), while attention was controlled by manipulating the validity of a motion cue that was briefly presented before the onset of target motion. While the individual subjects were performing the task, we recorded their eye positions using an infrared video tracking system (EyeLink 1000 Plus, SR Research, Ltd.), and measured EEG activity using a 64-channel active electrode system (BrainAmp, Brain Products, GmbH) for later analysis. Consistent with the previous study on non-human primates (Yang, Lee, and Lisberger, 2012), we found an interaction between direction prior and the strength of visual motion. Specifically, pursuit directions were attracted towards the prior direction especially when the visual motion was weak (12% contrast). In addition, attention appears to nullify the effect of the prior. When the direction cue was valid, pursuit directions were closer to the target direction even if the contrast of the pursuit target was low. A simple Bayesian observer model may explain the behavioral data if attention works on the likelihood function in such a way that it reduces the standard deviation of a Gaussian distribution.

**Disclosures:** **S. Kim:** None. **J. Lee:** None.

**Poster**

**493. Eye Movements and Perception**

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NIH U01EY025501

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**Title:** Is there tremor on the retinal image during active fixation?

**Authors: *N. R. BOWERS**, K. G. FOOTE, E. BENSINGER, K. RATNAM, A. E. BOEHM, A. ROORDA
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**Abstract: Introduction:** The study of fixational eye movements (FEM) has implications for the neural and computational aspects of visual perception. One component of FEM is tremor, a high frequency oscillatory jitter with an amplitude of a few seconds of arc. Tremor is often identified as an increase in the power spectrum of eye motion in a band of frequencies around 50-100Hz. The contribution of ocular tremor to visual perception is still not fully understood.
**Methods:** A novel eye tracking method using a Tracking Scanning Laser Ophthalmoscope (TSLO) was utilized to examine the characteristics of tremor on the retinal surface. The left eyes of 7 subjects were tracked while fixating a tumbling E. The contribution of ocular tremor to the retinal image motion was determined using spectral analysis of high resolution eye motion traces. The ability of the TSLO system to record high frequency motion and therefore detect tremor was validated in three ways: (i) spectral analysis methods were validated by analyzing synthetic eye motion traces composed of a tremor motion overlaid onto a random walk, (ii) eye motion traces and power spectra were computed from videos where high frequency motion was inserted digitally into real TSLO videos of a fixating eye, and (iii) eye motion traces and power spectra were computed from videos of a model eye with actual high frequency motion.
**Results:** The TSLO system was able to recover tremor in each of the three validation conditions. However, contrary to previous findings, the increase in power between 50-100Hz indicative of tremor was minimally apparent in the power spectra of motion on the retinal image of human eyes during active FEM. The amplitude of eye motion decreased monotonically as a function of frequency and, although there was a slight deviation from the typical 1/f pattern within the range of 50-100Hz, this increase never exceeded ~2 seconds of arc, much lower than previous reports of tremor.
**Discussion:** Most eye tracking methods that measure tremor rely on tracking the cornea or lens, and can only infer the movement of the image on the retina. The TSLO has the advantage of measuring the retinal image motion directly and unambiguously. The reported movement of the anterior segment of the eye induced by ocular tremor is greatly reduced at the level of the retina, and is therefore unlikely to contribute to the visual percept.

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**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 493.07/EE27

**Topic:** D.09. Visual Sensory-motor Processing

**Title:** The implications of near work on academic success

**Authors: *A. S. HOCHMAN**[1], D. A. DEL CID[2], N. URENDA[3], J. MIER[3], S. A. DREW[3]
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**Abstract:** Asthenopia or visual discomfort is a condition associated with near work tasks. Near work tasks consists of any task done within arms-length (i.e., texting, working on a laptop, reading a textbook). Individuals struggling with visual discomfort may experience symptoms such as headaches, blurred vision, and sensitivity to light. Due to the high demand on college students to perform near work tasks and the potential associated symptoms, we investigated whether visual discomfort had an impact on academic performance. Two oculomotor systems are involved in visual discomfort: the accommodation system and the vergence system. An insufficiency in either of these systems can be associated with visual discomfort. Two surveys have been developed to address insufficiencies in these systems. The Visual Discomfort Survey (Conlon et al., 1999) has been linked to accommodative insufficiencies and the Convergence Insufficiency Symptom Survey (Borsting et al., 2003) has been linked to insufficiencies in the vergence system. An academic problems survey was added to investigate whether visual discomfort symptoms are linked to perceived academic problems (Chase et al., 2009). We also wanted to assess an individual's ability to persevere despite their visual discomfort symptoms and we did this using the grit survey (Duckworth et al., 2007). Participants completed all four surveys and a demographic questionnaire. Results found that symptoms mediates the relationship between near work and academic problems. Ethnicity moderated the pathway between near work and discomfort and grit has a main effect on symptoms. These findings have widespread implications in the field of neuroscience, due to the dependency on computers and growing use of near work tasks it is important that we better understand visual discomfort. By better understanding visual discomfort and it's potential impact on students we can help find interventions to help students succeed in academics.

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**Poster**

**493. Eye Movements and Perception**

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** Tab Williams Family Endowment

**Title:** Parsing the contributions of perception, motor planning, and cognition to anti-saccade performance in human subjects

**Authors: *B. R. STEINBERG**[1], L. SUSSMAN[2], S. FRY[3], D. ANDERSON[1], C. K. HAUSER[1], E. SALINAS[1], T. R. STANFORD[1]
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**Abstract:** The anti-saccade (AS) task, which requires subjects to look ***away*** from a peripheral visual cue, is considered to be a sensitive assay of executive function. Its requirement to withhold responding to a salient, abruptly appearing visual cue in favor of programing a saccade to a diametrically opposed location is thought to rely heavily on frontal cortical mechanisms of cognitive control. However, as for all paradigms that begin with sensory input and end with motor output, it is a major challenge to discern the respective contributions of sensation, motor planning, and cognition to behavioral performance as typically measured in terms of accuracy and reaction time (RT). The present study deploys a novel task that combines the perceptual, motor and cognitive demands of the AS task with an urgency requirement in an effort to distinguish and quantify the relative contributions of these capacities to AS performance in human subjects. The Compelled Anti-Saccade (CAS) task required subjects to begin programming a saccade ***in advance*** and to use later arriving perceptual information about cue location to modify the ongoing motor plan. This urgency requirement generates a unique psychometric function — the tachometric curve — that tracks success rate as a function of perceptual ***processing time*** (PT), the interval between cue presentation and saccade onset. For the CAS task, the tachometric curve took on a characteristic shape that we interpret to reflect the interaction of perceptual (cue driven) and cognitive (internal planning). For PTs less than 50 ms, subjects performed at chance (50%), consistent with uninformed choices (guesses). However, PTs between 75-125 ms were associated with a pronounced dip to below-chance performance, which reflected the irrepressible “pull” of the salient stimulus that caused subjects to erroneously saccade to the cue. Performance recovery, a reflection of cognitively-guided motor planning, began at PTs of between 100-150 ms and was evident as a gradual rise in success rate as subjects directed a progressively larger proportion of saccades to the correct, “anti” location. The onset time and depth of the early PT performance dip assays the strength of low-level sensory

representations, and recovery from this perceptual vortex reflects the strength of cognitive mechanisms that resist its pull, perform the necessary mental rotation, and program an "anti-saccade". Together with RT distributions that independently assay motor function, the findings provide a detailed account of how a subject's perceptual, motor, and cognitive capacities interact in time to guide saccadic choice.

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**Poster**

**493. Eye Movements and Perception**

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NIH Grant EY019288

Human Frontier Science Program Grant

**Title:** Binocular alignment in mice during stereoscopic discrimination of depth

**Authors: *J. M. SAMONDS**[1], V. CHOI[2], N. J. PRIEBE[3]
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**Abstract:** In order for animals with binocular vision to use retinal image disparity to infer depth, they must be able to maintain some alignment between the eyes. Primates and carnivores frequently make coordinated saccades, and when they fixate on an object, their eyes converge or diverge to align their retinal images at that point. Rodents do not have a fovea, saccade less frequently, and their eyes are directed laterally at an angle of 50 degrees. Nonetheless, neurons in the primary visual cortex of mice are tuned for binocular disparity and mice have 40 degrees of binocular overlap. Therefore, we examined the binocular eye movements of head-fixed mice to see whether they could use this disparity tuning. During free viewing of natural scenes, mice nearly always made coordinated saccades. The eyes generally converged slightly relative to their average gaze during the saccade and diverged back to the original alignment while fixating. The range of relative vergence angles during free viewing corresponds to the expected range of useful binocular disparities for mice. We also examined binocular eye movements of mice while they discriminated between relative near and far surfaces rendered in dynamic random dot stereograms. For both near and far surfaces, the mice would start converging their eyes seconds before stimulus onset and then diverge their eyes back to the natural gaze position once making a decision about whether the surface was near or far. We analyzed the vergence angle for correct

and incorrect trials and found that successful discrimination required the eyes to be slightly converged with the same alignment for near and far surfaces. This suggests that mice can align their eyes and successful stereoscopic discrimination depends on proper binocular alignment.

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**Poster**

**493. Eye Movements and Perception**

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NIH R01-EY025648 (JG)

Alfred P. Sloan (JG)

**Title:** Dynamically tracking the neural signatures of visual attention across a saccade

**Authors:** ***J. CHEN**[1], X. ZHANG[2], J. D. GOLOMB[1]
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**Abstract:** To maintain visual stability, the retinotopic coordinates of objects need to be remapped across each saccade. Recent evidence suggests that visual attention is also remapped. Research has reported two different stages of remapping: a fast remapping to the new retinotopic location (i.e., predictive remapping of attention; Rolfs, Jonikaitis, Deubel, & Cavanagh, 2011) and a slower disengagement from the prior representation (i.e., retinotopic attentional trace; Golomb, Chun, & Mazer, 2008). While there is some behavioral evidence for both stages (Jonikaitis et al., 2013), it remains unclear the temporal and neural dynamics of how these two stages relate to each other, and more generally how the focus of attention is dynamically shifted over the entire perisaccadic period. In the current study, we recorded steady-state visual evoked potentials (SSVEP) in human EEG to dynamically read out which objects subjects were attending to across each saccade. Three orientation gratings were displayed on the screen with two possible fixation locations between them ("O+O+O" pattern). Subjects maintained attention on the central patch and reported an occasional orientation change. In half of the trials, subjects also made a saccade from one fixation point to the other as soon as a saccade cue appeared. Thus, the central patch was the spatiotopic (attended) location, while the other two patches represented the "predictive-remapping location" and "retinotopic-trace location", respectively. All three patches flickered at different frequencies, such that each location was tagged with a unique SSVEP spectral peak. Time-frequency analysis was performed on EEG data to calculate inter-trial coherence (ITC) corresponding to each location over time. ITC was greatest at the

spatiotopic (attended) location during baseline periods (outside the perisaccadic window), indicating that subjects were successfully attending to the spatiotopic location. Immediately before each saccade, the ITC difference between the spatiotopic location and predictive remapping location was reduced compared with the presaccadic baseline, suggesting attention temporarily shifted to the predictive remapping location. Immediately after each saccade, the ITC difference between the spatiotopic location and retinotopic-trace location was smaller compared with the postsaccadic baseline, consistent with a temporary lingering of attention at the retinotopic-trace location subsequent to each saccade. The current experiment provides a new method to dynamically track the neural signatures of visual attention across a saccade.

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**Poster**

**493. Eye Movements and Perception**

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**Title:** Correlated variability during eye movement planning in the frontal eye fields and superior colliculus

**Authors:** ***S. B. KHANNA**[1,2], U. K. JAGADISAN[2], A. C. SNYDER[3,1], N. J. GANDHI[2], M. A. SMITH[1]
[1]Dept. of Ophthalmology, [2]Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [3]Dept. of Electrical and Computer Engin., Carnegie Mellon Univ., Pittsburgh, PA

**Abstract:** Trial-to-trial fluctuations in spiking activity, which give rise to correlated variability, are commonly observed between pairs of neurons in a wide variety of cortical areas. When processing a visual stimulus, for example, the correlation among neurons has been suggested to impact the amount of information a given neuronal population can represent. This stored sensory information is often used to then guide a motor output such as an eye movement. Very little is known, however, about the correlated activity in areas that bridge this sensory and motor divide,

particularly the relationship between correlated activity and behavior. The frontal eye fields (FEF) and superior colliculus (SC) are both considered to be important regions controlling eye movements. Because both areas contain neurons with a wide variety of response profiles (both visual and motor), they are ideal candidates for studying the relationship between correlated activity and the planning and execution of eye movements. We used linear electrode arrays to record from groups of FEF or SC neurons in alert rhesus macaque monkeys performing a conventional memory guided saccade task (FEF) or delayed visually guided saccade task (SC). We measured the spike count correlation (also known as noise correlation) between pairs of simultaneously recorded neurons during the delay period, after the visual stimulus was present but before the animal had made an eye movement. We found correlation in this epoch leading up to an eye movement varied depending on the reaction time of the animal's subsequent eye movement in pairs of both SC and FEF neurons. Additionally, the relationship between correlation and reaction time was dependent on the direction of the eye movement. This correlation structure shared a number of common features between FEF and SC populations, while the observed differences may be understood by considering their different levels in the oculomotor hierarchy.

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**Poster**

**493. Eye Movements and Perception**

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NIH Grant EY022411

**Title:** Integrated representation of reward and sensory information in the macaque caudate during a perceptual decision

**Authors: *T. DOI**, Y. FAN, J. I. GOLD, L. DING
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**Abstract:** Decision making often requires processing uncertainty related to reward expectation and/or sensory input. For tasks with reward manipulations, some caudate neurons encode reward-related information, such as the reward context, reward expectation for a given choice alternative, and reward expectation for the chosen action. For tasks with sensory manipulations, some caudate neurons are modulated by the identity and strength of the stimulus. These diverse patterns of activity suggest that caudate neurons may combine reward and sensory information at a single-neuron level to support the selection and evaluation of choices. To test this hypothesis,

we recorded caudate activity in two monkeys performing an asymmetric-reward visual motion discrimination saccade task. For this task, the stimulus identity and strength are manipulated as motion direction and coherence, respectively, of a random-dot kinematogram, and reward context is alternated in blocks of trials such that, for a given block, one choice is paired with a large reward and the other is paired with a small reward.
Based on linear regression analyses, we found that ~60% of the recorded caudate units encoded both sensory and reward information, either additively or multiplicatively, during at least one task period. During stimulus viewing, “additive” neurons encoded the reward context as an offset of baseline activity, and “multiplicative” neurons showed reward-context modulation of how activity related to motion strength. After a saccade was made, the majority of “additive” neurons encoded reward expectations based on reward context and motion strength, but the fraction showing congruent modulation patterns (e.g., preferring large reward and stronger motion for both choices) was not above chance. Some neurons showed multiplicative reward size and coherence modulation consistent with reward expectation for both choices. We suggest that the caudate nucleus contributes to choice selection by integrating reward context as the baseline offset and by modulating accumulation rates during evidence accumulation. The caudate may also contribute to choice evaluation by providing signals that multiplicatively combine sensory and reward-size representations in a way consistent with the “common currency” idea.

**Disclosures:** **T. Doi:** None. **Y. Fan:** None. **J.I. Gold:** None. **L. Ding:** None.

**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 493.13/FF4

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** National Natural Science Foundation of China (Grant No.31471069)

Major Research plan of the National Natural Science Foundation of China(Grant No.91432109)

**Title:** Visual receptive field changes dynamically across saccade in macaque lateral intraparietal cortex

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**Abstract:** Primates perceive a stable visual world, unnoticed of the frequent displacement of retinal image caused by saccade. Since neurons in many brain areas encode spatial information

with their eye-centered visual receptive fields, the spatial reorganization of receptive fields around saccade may reveal the potential neural mechanism of visual stabilization. Previously, it is found that neurons in some brain areas respond in advance to visual stimulus which will be brought into their receptive field by an impending saccade. This anticipatory receptive field remapping may integrate the pre- and post-saccadic visual information, thus mediate visual stabilization. However, such theory has been challenged recently by findings that visual receptive field of most neurons in frontal eye field converged toward saccadic target instead of the location of future receptive field. Thus, there is an ongoing dispute regarding the function of perisaccadic change of visual receptive field: maintaining visual stability versus selecting saccadic target.
Here we recorded single neuron's activity extracellularly from macaque lateral intraparietal cortex (LIP) while monkeys were performing a modified visual-delay saccade task, in which a task irrelevant visual probe briefly flashed at various location of screen. Visual probe appeared at 4 epochs of the task, i.e., during fixation, during delay, just before saccade and long after saccade. We found that: 1) during delay period, while visual receptive field of minority neurons extended toward the location of future receptive field, visual receptive field of majority neurons expended toward the saccadic target. 2) just before saccade, visual receptive field of majority neurons expended toward the location of future receptive field, whereas visual receptive field of minority neurons expended toward the saccadic target.
Our results are consistent with previous findings of anticipatory receptive field remapping. In addition, we report a dynamic change of visual receptive field in LIP between delay period and just before saccade , which indicates the mixed function of LIP in spatial perception across saccades: target selection and visual stability.

**Disclosures:** **C. Zhang:** A. Employment/Salary (full or part-time):; full. **L. Yang:** None. **M. Zhang:** None.

**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 493.14/FF5

**Topic:** D.09. Visual Sensory-motor Processing

**Title:** Transsaccadic perception of moving objects

**Authors: *S. PRIME**, L. NEUBURGER
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**Abstract:** Most research on transsaccadic perception has focused on how static objects are spatially updated across saccades. Less is known about how and to what extent the visual system is able to keep track of the position of moving objects across saccades. Here, we investigated

how well subjects were able to detect when a moving object jumped either forward or backward along its motion path during a saccade. Subjects were presented with a dot stimulus moving with smooth continuous motion across a display as they maintained their gaze on a fixation point. Subjects were required to make a saccade when the fixation point moved to a different location. On some trials, the dot jumped forward or backward during the saccade. Subject made a 2AFC response to indicate if they detected a displacement or not. Based on previous findings showing that detection of intrasaccadic displacement of static stimuli is better with smaller displacements and saccade directions orthogonal to displacement direction (Niemeier, Tweed, and Crawford, 2003), we conducted a series of experiments where we systematically varied the displacement size and saccade direction relative to the dot's motion direction. Similar to previous findings with static stimuli, detection accuracy increased with displacement size, confirming that accurate transsaccadic motion tracking is also dependent on the amount of the intrasaccadic change in position. Although studies with static stimuli show a detection advantage for orthogonal saccades versus parallel saccades relative to the intrasaccadic displacement, we failed to find a similar advantage with moving stimuli. Instead, we found similar detection performance for all saccade directions, except significantly impaired detection when saccades were made towards the dot stimulus. We propose that the lower sensitivity in detecting displacements with saccades made toward the motion stimulus is consistent with evidence of spatial distortions in the area around the saccade target (Ross et al, 1997). Moreover, forward displacements were detected significantly less often than backward displacements, suggesting that the visual system is more likely to infer accurate post-saccadic target position and rely less on the internal computations extrapolating the future position of moving objects over the saccade when the displacement is in the direction of motion. These findings have important implications for incorporating motion tracking in models of transsaccadic perception.

**Disclosures: S. Prime:** None. **L. Neuburger:** None.

**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

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**Program#/Poster#:** 493.15/FF6

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** EXC307 (CIN - Werner Reichardt Centre for Integrative Neuroscience).

**Title:** The optokinetic response is maximally driven by stimuli located in the region of the retinal area centralis in larval zebrafish stimulated with a spherically surrounding stimulus arena

**Authors: *J. HINZ**[1,2,3,4], R. MEIER[2,3], F. A. DEHMELT[2,3], K. WANG[2,3], V. HAIKALA[5], D. REIFF[5], A. B. ARRENBERG[2,3]
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**Abstract:** The emergence of the larval zebrafish as a model organism in systems neuroscience has spawned a variety of data recording techniques and stimulation hard- and software. Computer screens and projection cylinders have been used as visual stimulus surface in the past. However, larval zebrafish have large visual fields, subtending about 160° in azimuth for each eye. Therefore, an ideal stimulus apparatus would present stimuli on the surface of a sphere to accurately cover the visual field of the fish. For the combination of calcium imaging with large-field stimuli it is advantageous to use LED arrays to temporally interleave visual stimulation and calcium indicator fluorescence recording based on the timing of the scanning mirrors of the microscope. Here, we present a stimulus arena consisting of 240 8x8 LED tiles that have been assembled in a sphere using a 3D-printed scaffold and are operated by microcontrollers via MATLAB. Together with a rotation mount and a glass bulb stage developed for larval fish, animals can be stimulated with stimuli covering up to 75% of the spherical surface in studies of whole-field gaze stabilization behavior, such as the optokinetic response (OKR) and the optomotor response (OMR). We are studying the neural circuits underlying these behaviors and wanted to identify which spatial locations drive the optokinetic response best. We placed larvae (5-7 dpf) in the middle of the sphere and presented horizontally drifting gratings (spatial frequency: 0.06 cycles per degree azimuth, sinusoidal velocity modulation with max. velocity of 12.6°/s and period of 10 s) that covered different visual angles (full-field, half-field, 60°-wide disks) and were positioned at different azimuths and elevations (36 different positions for the 60° masks). Animals responded with optokinetic behavior and we found that the OKR gain of larval zebrafish strongly depended on stimulus position. Animals maximally responded to stimuli located fronto-laterally above the equator, which roughly corresponds to the previously published temporal-ventral position of the area centralis of the larval retina. Potential explanations for our findings include a) superior motion detection performance in the area centralis or b) a behavioral preference to minimize retinal slip in the area centralis. Our finding has important implications for future study designs investigating the OKR in larval zebrafish and it stresses the often neglected importance of the area centralis in zebrafish vision.

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**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

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**Program#/Poster#:** 493.16/FF7

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** National Eye Institute Grant 5T32 EY017271-07

NIH Grant 1P50-MH103204

**Title:** Correlations in pre-saccadic frontoparietal activity: Are they conserved across spike-spike, spike-lfp, and lfp-lfp comparisons?

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**Abstract:** Neurons in both the dorsolateral prefrontal cortex (PFC) and posterior parietal cortex (PPC) of the macaque monkey are known to jointly encode the direction of a planned saccadic eye movement. With strong reciprocal connections it is likely that the two areas exchange information during saccade planning and execution. The dynamics of this exchange are not yet well understood. To explore this relationship we used linear microelectrode arrays to simultaneously record from PFC and PPC during the memory-guided saccade task. We analyzed the spiking data by calculating the Pearson's spike-count correlation coefficient of all cross-area neuron pairs. We previously found that (Hall et al., in prep) if two neurons were selective for the same location and if the monkey was required to make a memory guided saccade to that location, then, during the period accompanying the execution of the saccade, the spike-count correlation decreased.

In the current study we looked to see if this interaction is also revealed during analysis of correlations between the local field potentials (LFPs) and spiking activity and LFP-LFP activity across areas. We found a parallel of the spike-spike correlation results within analysis of the LFP-LFP interactions. Because the activity of more than one neuron can be recorded on a single electrode contact, we first defined the spatial selectivity of each LFP signal. Then we calculated the magnitude-squared coherence between the LFPs that were selective for the same location. We found significantly less coherence when the monkey was required to make a memory-guided saccade to the preferred location than to the non-preferred location. Interestingly, our preliminary calculations of spike-LFP coherence do not parallel the spike-spike and LFP-LFP correlations. Our spike-field analysis reveals little coherent activity around the saccade for both target locations.

A plausible interpretation is that during generation of an action, such as execution of a saccade, the areas interact through their reciprocal connections and an indirect executive control loop. The executive control loop could explain the observation of negative spike-count correlation and decreased LFP-LFP coherence, as well as the non-coherent spike-LFP activity between prefrontal and parietal neurons during execution of the saccade.

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**Poster**

**493. Eye Movements and Perception**

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**Program#/Poster#:** 493.17/FF8

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** U01NS094330

**Title:** Target selection for tracking eye movements in the common marmoset

**Authors: *N. J. PRIEBE**[1], J. PATTADKAL[2], J. KNÖLL[3], A. LEVI[5], H. CARNEY[4], A. HUK[6]
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**Abstract:** Pursuit eye movements allow the stabilization of moving objects on the retina by matching eye velocity to a selected target's velocity. This voluntary process requires target motion be separated from other motion signals in the world. This selection process has previously been linked to the acquisition of targets by saccadic eye movements in humans and macaques. Here we investigated if the common marmoset, a small New World primate, also exhibits changes in pursuit eye movements related to target selection. We measured tracking eye movements in two marmosets to motion of a single target or two targets, using the Rashbass step-ramp paradigm. In the single target task, animals were rewarded for successfully tracking a 4-6 deg/s moving target using a combination of saccades and smooth pursuit. In agreement with previous measurements in macaques (Lisberger, 1998), we found that a saccade to the target during pursuit initiation enhanced the amplitude of smooth pursuit (mean pre saccadic gain = 0.25, mean post saccadic gain = 0.74, gain = eye velocity/target velocity). Those trials in which saccades occurred early had a higher amplitude smooth eye velocity than those trials in which the saccade occurred late during initiation, but the gain during sustained pursuit did not depend on the saccade latency in this period. In trials in which two targets were presented, marmosets could track either target, and selection was marked by saccade direction. Saccade latencies were similar for single and two target conditions. The gain of pursuit eye movements increased following saccades to the selected target, and the presence of the second target nonetheless altered pursuit. We computed the weight of each target's influence on pursuit eye movements before and after saccades. Before the saccade occurred the weight of the two targets was near equal, consistent with a vector averaging computation being performed, whereas after the saccade occurred weights shifted to 0.68 for the selected target and 0.32 for the nonselected target. These results indicate that marmosets perform a similar selection procedure to track objects as other primates.

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**Poster**

**493. Eye Movements and Perception**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 493.18/FF9

**Topic:** D.09. Visual Sensory-motor Processing

**Title:** Tradeoff between expectations and evidence for visual continuity across saccades

**Authors: *D. SUBRAMANIAN**[1], Z. M. ABZUG[2], M. A. SOMMER[3]
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**Abstract:** The image of the external world is displaced across the retinas with every saccade, and yet our visual perception is coherent and continuous. We showed previously that the mechanisms of transsaccadic visual continuity are influenced by expectations about objects (Rao, Abzug, & Sommer 2016). If an object is not expected to move during a saccade but does, its movement is detected with higher visual sensitivity (d'). The real-world implication is that, for example, we would notice the transsaccadic movement of a rock more than a bird. We hypothesized that the system is Bayesian in the sense that the brain relies more on these priors when visual evidence is less certain. To test this, we ran human subjects (n=16) on a modified saccadic suppression of displacement task. On every trial, subjects fixated a central cross for a fixed duration, made a saccade to a peripheral target, and reported whether it had moved or remained stable during the saccade. The critical manipulation was to vary the quality of visual evidence (blurriness of the target) and determine if this affected the use of priors (expectation that the target would move). Each session consisted of two phases: training and testing. In the training phase, probability of target movement (10%, 50%, 90%) corresponded to the color of the fixation cross (e.g. red, white, green). Subjects were provided with trial-by-trial feedback on their performance in this phase. Targets were convolved with a very low-variance Gaussian blur (0.01 deg.) so that they appeared near-punctate. Subjects implicitly learned and used the color-associated priors about probability of target movement (confirmed by changes in d'). In the testing phase, two levels of visual uncertainty were introduced by convolving targets with low and high noise Gaussians (0.0625 and 0.25 deg. variance, respectively). Total luminance of all targets was constant. Fixation cross colors associated with 10% and 90% priors during training were randomly interleaved, although the actual probability of movement was 50% to isolate effects of the learned priors on subjects' responses. Supporting our hypothesis, we found that subjects relied on their learned priors significantly in the high noise condition but not the low noise condition. This reliance on priors was most prominent when subjects were least certain (near the 50% threshold level of psychometric curves; i.e. equally likely to report movement or

stability). We conclude that, consistent with a Bayesian framework for transsaccadic visual continuity, subjects rely on prior expectations about object movement more when the evidence is less reliable.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

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**Program#/Poster#:** 494.01/FF10

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** CBIR15MIG004

**Title:** Bold fMRI and somatosensory evoked potential response to electrical stimulation of tibial nerve: TBI pilot study

**Authors: *S. H. SALEH**[1], D. ALLEXANDRE[1], B. S. MAAS, 07052[2], D. A. CUNNINGHAM[3], A. HOXHA[2], G. H. YUE[4]
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**Abstract:** Damage to cortical and subcortical structures after traumatic brain injury (TBI) leads to many physical deficits. Electrical stimulation (ES) is conventionally used to test somatosensory evoked potentials (SEP) using EEG, and to stimulate muscle activity in functional ES interventions. However, brain activity in response to ES of peripheral nerves has not been studied in TBI survivors. In an ongoing study, we used ES to study SEP and brain excitability using EEG and fMRI. To date, we collected data from 6 individuals with disabilities due to TBI (age 56±4, 4 severe, 2 mild TBI); participants provided informed consents approved by Kessler Foundation ethical review board. ES was applied on the Tibial Nerve (medial malleolus), with a rate of 1.9Hz, and pulse width of 1 msec. The stimulus amplitude was individually adjusted to get a threshold that can be tolerated by the subject (uncomfortable but not painful) and induce consistent toe muscle twitching. In the EEG session, ES was applied continuously for 3 minutes on each foot. In the MRI session, ES was applied in 4 blocks (40 seconds rest, 20 seconds ES). ES on the left and right foot were applied in separate scan runs, duration of each was 5 minutes. fMRI data was collected using a 3T Siemens scanner (EPI sequence, TR=2seconds, TE=30ms, FA=90º) and MRI-compatible electrodes were used for ES. Preliminary fMRI results show activity in the following areas in response to Tibial nerve ES: bilateral posterior and anterior insular cortex, bilateral supramarginal and angular gyrus, bilateral thalamus, contralateral sensory and motor foot area, and contralateral supplementary motor area. These findings are consistent with studies that show a role of these regions in processing touch

and pain. Interestingly, two of the 6 TBI subjects (severe TBI) who require assistance to stand or use a cane to walk, did not show activity in the foot area during ES, and they did not show a strong SEP in the EEG experiment. In these participants, we noticed postcentral gyrus activity more lateral than the foot area, suggesting that TBI caused reorganization in the somatosensory networks of these individuals. While the data based on the small sample size are immature to make a conclusion about the relationship between TBI severity and excitability of somatosensory network during ES, the study is ongoing and additional data from newly enrolled participants may make the results more conclusive to help better understand the effect of TBI on somatosensory networks. The data may eventually help guide development of neuromodulation-based rehabilitation interventions to promote neuroplasticity for speedy and more complete recovery of sensorimotor function.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

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**Program#/Poster#:** 494.02/FF11

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** KAKENHI JP26112005

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KAKENHI JP16H01516

Brain/MINDS

**Title:** Characterization of sensory and motor representation across rodent sensory, association, and motor cortices

**Authors: *M. KAWABATA**, S. SOMA, A. SAIKI, J. YOSHIDA, A. RIOS, Y. SAKAI, Y. ISOMURA
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**Abstract:** The cerebral cortex, consisting of sensory, association and motor cortices, receives sensory information such as visual and auditory senses, and transforms it into motor information to control muscles appropriately. Although specific functions of these cortices have already been known individually, the whole picture of the sensorimotor transformation across them remains unclear at a single-cell level. Here, we characterized sensory and motor representations across the primary visual cortex (V1), posterior parietal cortex (PPC), and secondary motor cortex (M2)

in rats behaviorally responding to visual and/or auditory stimuli. The rats performed a behavioral task under head-fixation, in which they had to push a spout-lever with right forelimb quickly in response to a brief cue presentation (light and/or sound) to get reward water. The behavioral task repeated a block of trials with a light cue or with a sound cue alternately, and trials with both cues were added occasionally at random. We obtained multi-neuronal recording from the three cortical areas during their task performance. To compare sensory and motor representation among these cortical areas, we analyzed the functional correlation of spike activity with the behavioral task (using task relevance index) and the temporal preference of spike activity for the sensory cue or pull response (using cue-response preference index) in each neuron. We also examined the dependence of spike activity on the reaction time, sensory modality and combination, and test/correction. We found that PPC neurons represented motor (pull response), rather than sensory (cue), information predominantly as a group, which was very similar to M2 neurons, but not V1 neurons. Nevertheless, a considerable number of PPC and M2 neurons displayed an intermediate form of cue-response preference, implying their higher-order functions in sensorimotor transformation. Moreover, we found that V1 neurons sometimes represented motor information in the spike increase evoked by the visual cue, suggesting that sensorimotor transformation might begin in the primary sensory cortex. Our results suggest that sensorimotor transformation is widely spread across cortical areas for functional integration and processing of information.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

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**Program#/Poster#:** 494.03/FF12

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** Swedish Research Council 2016-03134

**Title:** Interrogating sensorimotor circuits of orientation: From lamprey to mouse

**Authors: J. PÉREZ-FERNANDEZ**, S. GRILLNER, *A. A. KARDAMAKIS
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**Abstract:** (Re)directing our line of sight in space is a function of the stimulus, internal state and our task at hand. These sensory-based decisions for gaze reorientation involve the complex interaction of several brain areas, including the active engagement of subcortical and cortical circuits.
Over the past years, we have explored tectal function by using a conserved vertebrate system, the

lamprey, as a reductionist organism that has offered the necessary accessibility allowing the development of a series of preparations for the study of sensorimotor control for gaze reorientation at the cellular and circuit level. In particular, by focusing on the conserved brain area essential for multisensory integration and motor control of orientation, the optic tectum, we found a dual motor response system within its deeper layers that contains projections neurons that target contralateral and ipsilateral brainstem zones causal to orienting and avoidance gaze movements, respectively. These neurons receive two types of sensory inputs, vision and electroreception (in lamprey), which converge onto each projection neuronal subtype with spatiotemporal correspondence. These computations are elaborated by a well-organized local GABAergic network within the superficial and intermediate layers of tectum, thus, mediating disynaptically multisensory inputs and projection neuron output controlling gaze.
Following this phylogenetic model, the circuit configuration giving rise to these rules we postulate to be similar in later vertebrates. We are now testing the validity of this prediction in the superior colliculus by using mice as a generic mammalian model. To do this, we are using Cre-dependent mouse lines (VGlut & VGat) combined with tools that include electrophysiology, optogenetics and motor behaviour. Our results show the striking similarity of this conserved dual motor system arising from glutamatergic projection neurons located in the deep layer and terminating in the pontine reticular formation along with the functional impact of these connections with and without local inhibition. Our overarching aim is to use circuit comparisons across a greater range of taxa by following the phylogenetic model to connect them and infer basic principles of sensorimotor integration.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

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**Topic:** D.09. Visual Sensory-motor Processing

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NBRC core funds

**Title:** Deactivation and activation of dorsal visual information processing pathway gates perception-action coupling

**Authors: *D. RAY**, N. HAJARE, A. BANERJEE
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**Abstract:** Dual stream hypothesis is a pre-eminent theoretical approach to conceptualize visuo-motor information processing. Subtle variations of the model exist often leading to fundamentally divergent explanations of underlying neural mechanisms. For example, the Mishkin-Ungerlieder (MU) model suggest that the *input* information decides the neural pathway for processing. Position related information ('where') takes the dorsal stream comprising MT/V5 and parietal cortex whereas finer feature processing ('what') comprising color, face, etc. takes the ventral stream involving V4 and inferior temporal areas. Concomitantly, the Milner-Goodale (MG) model suggests that the task *goal* decides the processing pathway, with dorsal stream areas needed for visual (sensory) guidance of action that doesn't involve active perceptual processing whereas the ventral stream is recruited for perceptual object processing. No single study has evaluated the viability of each model in a overarching experimental design. Furthermore are the models subject to neuroplastic changes is an open question.

We addressed these issues in an fMRI experiment involving 20 right-handed human volunteers (20-34 years, 12 females). Participants were scanned with TR=2 s TE= 35ms, flip angle =90° while each of them was performing 3 visual perception tasks and 3 visuo-motor action tasks inside a 3T MRI scanner. For both categories, 2 tasks were designed to involve "what" (color, face) processing and 1 task required processing of "where" (position) information. The fMRI scans were repeated after seven days of the practice session outside the scanner to explore the neuroplastic changes.

In all perception tasks, bilateral ventral stream areas are activated, whereas all action tasks shows prominent activations in bilateral primary visual cortices, ventral and dorsal stream regions. Unlike color and face perception, position perception elicits additional activations in dorsal stream areas. Deactivation of BOLD signals were observed in medial dorsal stream areas and in few primary visual and ventral stream regions. Analysis of reaction times established the positive effect of practice. Number of voxels activated decreased with practice but no such decrease was observed for deactivated voxels.

Dorsal stream activations in orientation perception could not be explained by the MG model whereas ventral stream activation in same condition violated the MU model predictions suggesting the need for a coupled perception-action model of visual processing. Deactivation found in perception tasks further points towards the role of feedforward and feedback interactions between both streams.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

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**Program#/Poster#:** 494.05/FF14

**Topic:** D.09. Visual Sensory-motor Processing

**Title:** Functional cell type specific expression of immediate-early genes in mouse visual cortex

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**Abstract:** Immediate-early genes (IEGs) have been indicated in neuronal plasticity events and play a critical role in visual development. Using transgenic mice expressing GFP under IEG promoter control, we chronically recorded both neural activity (using a red shifted calcium indicator) and IEG expression levels during visual development in primary visual cortex. Animals were born and reared in complete darkness and we imaged calcium activity and IEG expression levels every 12h over the course of 6 days both before and after first visual exposure. On the first two days activity in V1 was recorded in complete darkness while mice were head-fixed and free to run on a spherical treadmill. On the third day of imaging we exposed them to visual feedback (first light exposure) in a virtual reality tunnel in which visual flow was coupled to the locomotion of the mouse. Outside of the imaging sessions mice were still housed in complete darkness. Starting on day 5 mice were then subjected to a 12/12h light/dark cycle. We found that IEG expression levels only weakly correlate with average neuronal activity, but expression patterns exhibited changes both at the onset of first visual exposure and light cycle onset. We also found that different IEGs are preferentially expressed in different functional cell types in layer 2/3 of mouse visual cortex. Neurons that exhibit strong motor-related activity express higher levels of EGR1, while neurons that exhibit visually driven activity express higher levels of Arc. These findings suggest that different IEG expression levels might correlate with plastic changes in the functional type of input a neuron in layer 2/3 receives.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 494.06/FF15

**Topic:** D.09. Visual Sensory-motor Processing

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**Title:** Previous trial effect in visuomotor integration depends on an implicit short-term memory mechanism in premotor cortex and hV5/MT+

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**Abstract:** The so-called previous trial effect has been reported from perception to motor output in human behavior. For example, the speed from previously experienced moving targets biases movements on the current trial in coincident timing tasks. The precise mechanism underlying the previous trial effect is still under debate. In the present study, we tested the hypothesis that previous encounters with moving targets leave a neural trace of the information experienced, i.e. an implicit short-term memory mechanism. This information could be stored in either premotor or visual areas associated with the task, and influence neural processing of the current trial. We assume that injecting noise by means of transcranial magnetic stimulation (TMS) would interfere and degrade such short-term memory and hence reduce or abolish the previous trial effect if TMS is applied over neural sites involved in the mechanism. To test this hypothesis and to identify brain regions involved in mediating the previous trial effect, we asked healthy participants (n = 20) to perform a coincident timing task and applied a burst of TMS pulses (10 Hz) 500 ms into the inter-trial interval and 3500 ms before the next trial to disrupt the activity in right hV5/MT+, in left dorsal premotor cortex, and in the control position Vertex. Trial speed was counterbalanced in a way that allowed every speed to be equally often preceded by all speeds. As expected, participants presented a bias towards the speed of previous trial when intercepting moving targets without receiving TMS pulses. TMS applied over dorsal premotor cortex decreased the previous trial effect in comparison to Vertex stimulation. TMS applied over hV5/MT+ decreased the temporal bias only mildly, reaching significance when compared to

performing the task without TMS, but only a trend when compared to Vertex stimulation. These results provide causal evidence that the previous trial effect is mediated to a large extent by inter-trial interval activity in the left dorsal premotor cortex, and to a lesser extent by right hV5/MT+, in a visuomotor integration task with moving objects. Absence of difference in overall timing error between TMS sites indicates that the TMS pulses did not affect processing on the current trial. This suggests that an implicit short-term memory mechanism keeps information from one trial to the next, and that this information — motor or visual — is blended with current trial information so that it biases behavior.

**Disclosures: R.M. De Azevedo Neto:** None. **E. Amaro:** None. **A. Bartels:** None.

**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 494.07/FF16

**Topic:** D.09. Visual Sensory-motor Processing

**Title:** Vergence responces induced by Radial flow motion visual stimulus in monkey

**Authors: *Y. KODAKA**
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**Abstract:** Radial flow motion with sigmoidal contrast circular pattern induced the vergence eye movement in monkey. Expansion motion induced the increasing vergence angle and the motion toward the contraction induced the decreasing vergence angle response with short latency. The Opposite direction of the vergence eye movement was induced by the Missing Fundamental pattern motion stimulus, which was also induced in Human subject (Kodaka et al., 2007). The response to the radial flow motion induced with the short latency (<100ms) and the Gain of the response show the contrast dependency and spatial frequency dependency. The threshold of the contrast dependency was 2 -4 %, which was little bit higher than the human data (0.5 -1%). These characters of the response are very similar with the human data. Our result suggests that the vergence response system in monkey has the similar visual information processing in human, and the monkey can use for the human visual process model.

**Disclosures: Y. Kodaka:** None.

**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

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**Title:** The primordial cortical microcircuit: Cytoarchitecture and sensory input

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**Abstract:** The lamprey lateral pallium, corresponding to the mammalian cortex, is conserved in terms of its efferent connectivity, with projections to the basal ganglia and the brainstem (Ocaña et al., 2015). Here, we delineate the architecture of pallium and examine visual and olfactory input.
The lamprey has a three-layered pallium with a molecular layer and a cellular layers. The innermost layer contains a high density of GABAergic cells and an almost equal number of presumed glutamatergic cells, while in the outer cellular layer the glutamatergic cells dominate. 22% of the cells are GABAergic. Calbindin- and calretinin-expressing cells are well represented in the innermost layer. The glutamatergic projection neurons (PT, pyramidal tract, IT, intratelencephalic and Th-r, thalamo-recipient cells) are located in the cellular layer and their spiny dendrites extend into the molecular layer. Thalamic input reaches PT-type cells polysynaptically, and to Th-r cells monosynaptically. The PT-type cells are concentrated in the dorsolateral parts of pallium and the Th-r cells are present in its ventral part.
Primary visual is relayed to pallium via thalamus, along with processed visual information from pretectum/tectum. Extracellular multi-unit recordings showed that neurons in the dorsomedial pallium are activated by input from the retina - "visual" pallium. This visual region is separate from pallial motor regions. Stimulations of specific retinal quadrants elicited response in separate visual pallial areas, indicating possible retinotopic organization. Local injections of gabazine in the visual pallium resulted in the loss of this retinitopic organization indicating that the

GABAergic neurons are responsible for maintaining specificity. Whole-cell recordings of pallial neurons during optic nerve stimulation elicited EPSP's and recruited inhibition.
Olfactory bulb input to pallium is relayed through two routes – directly and via a relay nucleus (dmtn), both of which traverse in distinct layers in the molecular layer. Large areas of pallium respond to extracellular stimulation of the olfactory nerve including motor regions. Moreover, olfactory input to pallial neurons is monosynaptic.
The lamprey pallium, thus has a three-layered microcircuit *bauplan* that includes many features of the three-layered reptilian cortex, the mammalian olfactory cortex and the neocortex and can be regarded as a primordial vertebrate cortex. This in turn means that the origin of the layered cortex can be moved back from the currently assumed reptilian cortex, to the very dawn of vertebrate evolution, when the lamprey diverged from the main vertebrate line over 500 million years ago.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 494.09/FF18

**Topic:** D.09. Visual Sensory-motor Processing

**Title:** The lateral parabrachial neurons contribute to pain-respiratory coordination in pons-medulla-spinal cord preparation

**Authors: *S. TONOMURA**[1,2], M. TANAKA[2], K. NOGUCHI[1], A. ARATA[2]
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**Abstract:** The sensation of pain signals projects to the lateral parabrachial nucleus (LPB) of the pons via the dorsal horn; and LPB is also known as the system of inspiratory-expiratory (I-E) phase switching; that contributes to the control of respiratory rate. Previous study reported that increase respiration was observed after noxious stimulation in humans. Thus, the tightly interaction between respiration and pain signals as a pain-respiratory coordination were expected in LPB. In this study, we investigated the pain-respiratory coordination system using the pons-medulla-spinal cord preparation intact forelimb (including Th1 level) isolated from postnatal 0-4 days-rats. Spontaneous inspiratory activity was recorded from cervical 4$^{th}$ (C4) ventral nerve root. And then we examined the responses of C4 activity when a small amount of 2% capsaicin was injected into forelimb as a noxious stimulation. The C4 inspiratory rate increased significantly with noxious stimulation in the preparation with pons, but removal of pons had no effects ($P < 0.01$). Moreover, we examined the properties of LPB neurons in the pons-medulla-spinal cord preparation. First, the responded area of LPB from C8 dorsal root stimulation was

detected by optical imaging using voltage-sensitive dye; then the LPB neurons (n=32) were recorded from the responded area using whole-cell patch-clamp. Three of 32 LPB neurons were I-E neurons which were synchronized with I-E phase of C4 ventral root activity. The other type of neurons (n=29) were spontaneous or non-spontaneous firing neuron which were not synchronized with C4 activity; so-called non-respiratory neurons. All I-E neurons and 8 non-respiratory neurons, which existed in the responded area by optical imaging were received excitatory input from C8 dorsal root stimulation. Each neuron tested current-voltage (I-V) relationship in current clamp mode. According to the responses of hyperpolarizing current pulses, post-inhibitory rebound (PIR) was observed in 13 non-respiratory neurons. These results suggested that 1) the pons contribute to increase of respiratory rate by noxious stimulation; 2) I-E neurons could directly receive noxious information, so I-E neurons were thought to be the core mechanism of pain-respiratory coordination; 3) the non-respiratory LPB neurons which expressed PIR might be contributed to the onset-switching mechanism of the pain-respiratory coordination network.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

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**Program#/Poster#:** 494.10/FF19

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NIH Grant P01HD064653

**Title:** Intranasal oxytocin enhances EEG mu rhythm desynchronization during execution and observation of social action

**Authors: *F. FESTANTE**[1,2], P. F. FERRARI[1,3], S. G. THORPE[2], R. W. BUCHANAN[4], N. A. FOX[2]
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**Abstract:** Intranasal administration of the hormone oxytocin (OT) facilitates prosocial behaviors, emotion recognition and cooperation between individuals. Recent electroencephalography (EEG) investigations have reported enhanced mu rhythm (8-13Hz) desynchronization during the observation of biological motion and social stimuli or during tasks that require social coordination in a dyad, after the administration of intranasal OT. It has also been hypothesized that this social hormone may target specific cortical circuits involved in

higher cognitive functions, which might include the Mirror neuron system (MNS). However, this hypothesis remains still largely unexplored. Here, in a double-blind, placebo-controlled, between-subjects study, we investigated whether intranasal OT might modulate the cortical activity from sensorimotor areas during the observation and the execution of social and non social grasping actions. Thirty-five adult male subjects participated in the study after being randomly and equally assigned to the OT (N=17) or the control (CT, N=18) group. Participants underwent EEG testing 45 minutes after receiving 24 IU of either intranasal OT or saline solution (Placebo). Each subject completed a visuo-motor task which included a social and a non-social condition. Both conditions started with the grasping of an object while they differed for the final goal of the action. In the social condition the grasping action was aimed at giving the grasped object to another person; while in the non-social condition the grasped object was placed into a container. During the observation task, participants observed video clips depicting the two types of action. During the execution task, subjects performed social and non-social grasps themselves. EEG mu power in the 8-13 Hz frequency band was computed by means of a Fast Fourier Transform. Results revealed greater mu desynchronization in the social condition compared to the non-social condition in the OT group, especially over central (C3, C4) and parietal (P3, P4) electrodes, although a modulation of mu frequencies was observed also across the scalp. No differences between the social and the non-social condition were found in the CT group. These results suggest a possible action of intranasal OT on sensorimotor circuits involved in social perception and action understanding, thus facilitating the possible prosocial effects typically reported by other studies.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

**Location:** Halls A-C

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**Program#/Poster#:** 494.11/FF20

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NIH Grant R01NS085122

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**Title:** Effect of target-directed movements on mirror visual feedback processing in ipsilateral brain areas

**Authors: *T. MANUWEERA**[1], M. YAROSSI[1], S. H. SALEH[2], S. V. ADAMOVICH[3], E. TUNIK[4]
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Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ; [4]Dept. of Physical Therapy, Movement, and Rehabil. Sci., Northeastern Univ., Boston, MA

**Abstract:** In persons with hemiplegia due to stroke, mirror visual feedback (MVF) of movements performed with the unaffected limb can recruit brain areas controlling the stroke-affected limb, potentially facilitating recovery. Given evidence that target-directed movements, relative to target-free, elicit stronger bilateral activation, we ask here if target-directed training with MVF may likewise elicit stronger activation in the untrained hemisphere. Following informed consent, 20 healthy subjects performed finger flexion movements using their dominant right hand, with feedback presented in a virtual environment (VR). Visual feedback was presented in real time VR as either veridical feedback with (VT+) and without (VT-) a target, and MVF with (MT+) and without (MT-) a target. Functional Magnetic Resonance Imaging (fMRI) contrasts (FDR-corrected) revealed significant activation in the ipsilateral intraparietal sulcus for the main effect of MVF and significant bilateral superior parietal activation for the main effect of target. Importantly, we noted significant and robust activation lateralized to the ipsilateral parietal cortex in the MT+ contrast with respect to the other conditions, suggesting that combining MVF with targeted movements may redirect bilateral activation to ipsilateral visuomotor processing areas. These findings may have important implications for understanding how it may be best to deliver MVF for rehabilitation purposes.

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**Poster**

**494. Sensorimotor Transformation: Neuroprocessing**

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**Title:** Visual and motor deficits in grown-up mice with congenital zika virus infection

**Authors: *L. CUI**[1], P. ZOU[1], E. CHEN[1], H. YAO[2], H. ZHENG[1], Q. WANG[1], J. ZHU[3], S. JIANG[1], L. LU[1], J. ZHANG[1]
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**Abstract:** Human infants with congenital Zika virus (ZIKV) infection exhibit a range of symptoms including microcephaly, intracranial calcifications, macular atrophy and arthrogryposis. More importantly, prognosis data have lagged far behind the recent outbreak of ZIKV in 2015. In this work, we allow congenitally ZIKV-infected mice to grow into puberty. These mice exhibited motor incoordination and visual dysfunctions, which can be accounted by anatomical defects in the retina and cerebellar cortex. In contrary, anxiety level of the ZIKV-infected mice is normal. The spectrum of anatomical and behavioral deficits is consistent across different mice. Our data provided evidence that may help predict the public health burden in terms of prognosis of ZIKVrelated congenital brain malformations in an animal model. Our study provided behavioral evaluation for the prognosis of congenital ZIKV infection and provides a platform for screening and evaluation of drugs candidates and treatment aiming at improving regeneration of infected neurons to prevent sequelae caused by ZIKV infection of fetus.

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**Poster**

**495. Visually-Guided Reaching**

**Location:** Halls A-C

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** ANR-11—LABEX-0042 grant from the University Claude Bernard Lyon within the program "Investissement d'Avenir" to A.S

**Title:** Brain areas involved in consciousness of a sensorimotor conflict

**Authors: *M. CORAZZOL**[1], G. LIO[2], A. SIRIGU[2]
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**Abstract:** The ability to correct our movements is fundamental for motor learning. This competence is under the control of a conscious action-monitoring system. However, motor compensation does not always need consciousness. For instance, subjects show limited or no consciousness at all when experiencing a mismatch between vision and proprioception. Here we investigated neural changes associated with a sensorimotor conflict (SMC) while subjects shifted from unconscious to conscious states. We asked participants (N=20) to draw a straight line on a graphic tablet without seeing their hand and to look at the unfolding trajectory on the screen. Angular perturbations were visually introduced thus forcing subjects to modify their movement in order to maintain a straight line. After each trial participants reported if they felt a perturbation. Using a staircase procedure, we computed subjects' detection threshold of the SMC. EEG recordings were acquired simultaneously to estimate the cortical sources involved in the unconscious to conscious transition of movement correction. Our results show that the supplementary motor area (SMA), the visual cortex (V3A) and the medial parietal cortex are involved in action monitoring during a sensorimotor conflict. Interestingly, the SMA and area V3A were found to correlate with movement correction. In particular, while activity of the SMA encoded the magnitude of the proprioceptive error, V3A reacted to the visual perturbation regardless of hand position. Importantly, medial parietal cortex did not encode specific movement features but activity in this area was principally linked to subjective awareness of the sensorimotor conflict. Our findings suggest that the medial parietal cortex is a key area for bringing movements into consciousness.

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**Poster**

**495. Visually-Guided Reaching**

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**Program#/Poster#:** 495.02/GG1

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** STW 12160

**Title:** Action decisions correlate with visuo-haptic matching errors

**Authors: *I. A. KULING**, J. B. J. SMEETS
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**Abstract:** People make systematic errors when matching the location of an unseen index finger with the location of a visual target. These visuo-haptic matching errors are idiosyncratic [1,2] and consistent over time [2]. So far, it is unknown whether and how these perceptual mismatches directly influence action decisions.
In this study, participants were asked to reach towards the closer of two visual targets with the index finger of their unseen hand from a varying unseen starting position. We hypothesized that the visuo-haptic matching errors would be reflected in the action decision on reaching to the closer target as a shift in the psychometric curve. Our results support this hypothesis since there is a correlation between the visuo-haptic matching error and the shift of the action decision.
Two additional findings are worth mentioning. For the outer starting positions participants are more likely to reach to the visual target that is closer to the center of the screen. This might be a visually induced bias towards the center of the screen, or a bias in the action decisions towards the body midline. Secondly, when comparing the steepness of the psychometric curves with the variability found in the matching errors to the target, variability of the decisions were lower than those of matching, in line with other visuo-haptic matching studies [1,2] and in action decision studies [3]. This combination of results suggests that position matching is less based on a prior than actions decisions are.
The results from this study suggest that visuo-haptic matching and action decisions use the same visual and proprioceptive information, but different priors.
1. Kuling, I.A., Brenner, E., & Smeets, J.B.J. (2013). Proprioception is robust under external forces. PLoS One, 8(9), e74236.
2. Kuling, I.A., Brenner, E., & Smeets, J.B.J. (2016). Errors in visuo-haptic and haptic-haptic location matching are stable over long periods of time. Acta Psychol 166, 31-36.
3. Nashed, J.Y., Crevecoeur, F., & Scott, S.H. (2014). Rapid online selection between multiple motor plans. Journal of Neuroscience, 34(5), 1769-1780.

**Disclosures: I.A. Kuling:** None. **J.B.J. Smeets:** None.

**Poster**

**495. Visually-Guided Reaching**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 495.03/GG2

**Topic:** D.09. Visual Sensory-motor Processing

**Title:** Contrasting effects of exogenous attention on saccades and reaches

**Authors: *A. MALIENKO**, A. Z. KHAN
Univ. De Montréal, Montreal, QC, Canada

**Abstract:** Planning saccades or reach movements to a specific location in the environment relies on attentional mechanisms to select a relevant location and on motor systems to correctly guide

the movements to their destination. However, it remains unknown whether movement planning of different effectors, eyes or arm, interacts with a single attentional mechanism or whether there exist multiple attentional selection mechanisms that are specific to the different effectors.
To test these two alternative hypotheses at the behavioural level, we recruited 13 participants (M = 22.8, SD = 1.5) to perform a task involving exogenous attentional allocation and movement planning. The participants were asked to fixate and hold their hand at an initial position on a screen in front of them (left or right of screen centre) and then, at the disappearance of the fixation cross, perform an eye or arm movement, or both, to a target square (mirror location of fixation cross). A distractor appeared momentarily just before the appearance of the target at one of seven equidistant locations on the horizontal meridian. Saccade reaction times (SRTs), reach reaction times (RRTs) and amplitudes were calculated.
Compared to the neutral condition (no distractor was presented), distractors overall did not result in a facilitation of SRTs at any location (shorter SRTs), rather only a strong inhibition (longer SRTs) as a function of distractor-target distance. In contrast, RRTs showed strong facilitation at the target location and less inhibition at further distances. However both SRTs and RRTs followed a similar pattern in that RTs were shortest closer to the target position and were increasingly longer as a function of distractor-target distance. In terms of amplitude, there was no effect of the distractor on reach endpoints, whereas, for saccades, there was an averaging effect of distractor position on saccade endpoints, but only for saccades with short SRTs. These effects were similar when either effector movement was performed alone or together.
These findings suggest that attentional selection mechanisms have both similar and differential effects providing evidence for both effector-independent and effector-dependent attentional selection mechanisms. This study provides understanding of the operating mechanisms of attention on eye and arm movements and the interaction between sensory and motor systems.

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**Poster**

**495. Visually-Guided Reaching**

**Location:** Halls A-C

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**Program#/Poster#:** 495.04/GG3

**Topic:** D.09. Visual Sensory-motor Processing

**Support:** CIHR

**Title:** Coordination of eye, head and hand movements during visually guided reaching in head unrestrained Rhesus monkeys

**Authors: *H. K. ARORA**[1], V. BHARMAURIA[2], X. YAN[2], H. WANG[2], S. SUN[2], J. D. CRAWFORD[2]
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**Abstract:** Non-human primates have been used extensively as animal models for human eye-head coordination and eye-hand coordination within a 2-D plane, but the more natural condition of eye-head-hand coordination during a 3-D reach has not been studied in monkeys. Our goal here was to determine if reaching influences eye-head coordination, and vice versa, in the monkeys. Eye, head, and hand motion were recorded in two rhesus monkeys using search coil and touch screen technology, respectively. Animals were seated in a customized 'chair' which allowed the head to move freely and the hand to reach in both depth and direction. In the standard reach condition, monkeys were trained to initially touch a central LED at the waist level and maintain gaze for 400-800 ms on a central fixation point. When the fixation light was extinguished, animals were required to reach toward a target appearing at one of 15 locations in a 40° horizontal x 20° vertical (visual angle) array. In other conditions, initial hand and gaze position were varied in the horizontal plane. Animal were rewarded for touching the target, but otherwise allowed to move the eyes and head freely. The gaze- control condition, animals were rewarded for fixating the target for variable durations in the same conditions with the reach blocked. Preliminary observations included: 1) animals generally produced coordinated eye-head gaze shifts toward the reach target and then maintained fixation until it was touched, 2) saccade reaction times reduced from means of 185/131 ms in the gaze control to 152/109 ms in the reach condition in animals A/B respectively, and 3) the head moved more in the reach condition for some targets, especially in the vertical dimension, as if it was disinhibited and/or driven more by gaze position during reaches. These data suggest that reach influences gaze kinematics, and will be further quantified to provide a more complete spatiotemporal description.

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**Poster**

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** UWM Office of Undergraduate Research SURF Funding

**Title:** The effects of varying cognitive and motor demand on an attention-mediated reaching task in older adults

**Authors: *L. PETROVSKA**, C. FUEGER, W. E. HUDDLESTON
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**Abstract:** Every day, vision guides one's actions to facilitate successful navigation through a complex environment. The efficiency of how our visual and motor systems interact may decline with age. We examined the effects of increased cognitive and motor demand on behavior during an attention-mediated reaching task. We hypothesized that as cognitive and motor load increased, performance would decline at a greater rate for older participants. Thirty-one healthy older adults (67-84 years, 8 females, 3 left handed) and twenty healthy younger adults (20-29 years, all female, 1 left handed) participated. The trial sequence was as follows: a brief location cue in 1 of 8 peripheral targets presented on a screen in front of the participants, a delay, and a central go cue. Participants performed each of two trial types. The first was a simple reach (SIMPLE) to the previously cued location. The second involved touching a target 3 locations clockwise from the initial cue (SPatial REmapping; SPRE). Participants performed the 2 types of delayed reaches under 4 task conditions. The two BASELINE conditions included either only SIMPLE or SPRE trials. The CHOICE condition included both trial types. The final condition was the same as CHOICE; however, during the delay participants touched 4 cued targets (i.e., a motor mask; MOTOR). Generally, older adults were slower in both reaction times ($F(1,48) = 25.10$, $p < .001$) and movement times ($F(1,48) = 31.73$, $p < .001$) in all trial / task conditions, with a significant group by task interaction (RT $F(2,47) = 6.46$, $p = .003$; MT $F(2,47) = 4.20$, $p = .021$). Conversely, older adult reach endpoints were more accurate ($F(1,48) = 15.41$, $p < .001$), and were less variable ($F(1,48) = 16.61$, $p < .001$), than the younger adults; while path lengths were not significantly different ($p>.05$). Thus, increases in both cognitive and motor load significantly and negatively influenced older adults' temporal performance to a greater degree than the younger adults. These results show that strategies to mitigate movement-related injuries in this population should consider task difficulty, and perhaps temporal constraints, as a rehabilitation strategy.

**Disclosures: L. Petrovska:** None. **C. Fueger:** None. **W.E. Huddleston:** None.

**Poster**

**495. Visually-Guided Reaching**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 495.06/GG5

**Topic:** D.09. Visual Sensory-motor Processing

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F32 NS076206

**Title:** Single-units in the lateral intraparietal area (LIP) distinguish between different patterns of unimanual and bimanual arm movements

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**Abstract:** Neurons in LIP, an area in the macaque posterior parietal cortex, robustly code saccade direction under many but not all conditions (Mooshagian et al., SFN abstract, 2016). Firing of individual neurons has been shown to be affected by contralateral arm movements, and this has been taken to imply a role in eye-hand coordination (Hagan et al., 2012). We recorded from single LIP neurons while animals made visually-guided saccades, combined saccade and reaches with either the left or right arm to a single target, or reaches with both arms to one or two targets. We find that at the population level, activity is slightly higher when the contralateral arm moves into the receptive field along with the eyes compared to a saccade without a reach. Ipsilateral arm movements have very little effect on population activity, alone or in combination with a contralateral arm movement. At a single cell level, however, a subset of cells respond differently to different movements, such that a support vector machine can distinguish each type of movement. Thus, information about complex patterns of reaches is present in LIP, although the net effect on neuronal firing is modest.

**Disclosures: E.F. Mooshagian:** None. **C.D. Holmes:** None. **L.H. Snyder:** None.

**Poster**

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NSERC discovery grant #05336 (LS)

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**Title:** Don’t watch where you are going: Cognitive-motor integration development in children and adolescents

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**Abstract:** The spatial locations of guiding sensory information and the required motor action are often in alignment, representing a direct interaction task. However, once we decouple vision and action, they can be misaligned, e.g., when reaching for an object from memory while looking away, or using a computer mouse. This ability requires rule-based visuomotor transformations,

or “cognitive-motor integration” (CMI), often used in every-day life. Both cognition and motor development in the young brain have been fairly well characterized. However, it is not known when and how the ability to control rule-based, decoupled action emerges. Here we investigate CMI development by measuring direct and decoupled visuomotor control across a range of ages. We hypothesize that the rate of CMI development will be constrained by cognitive development rather than motor development, given the later development of cognitive spatial versus goal-directed reaching abilities in children. The actual age of CMI maturation is an exploratory question. Youth in two age groups (children, n=29, 8-12 yrs, mean 10 yrs; adolescents, n=33, 13-15 yrs, mean 14 yrs) performed two eye-hand coordination tasks. In the direct interaction task, participants slid their finger on a vertical touchscreen to move a cursor from a central target to one of four peripheral targets. In the CMI task, targets were in a different plane from hand motion, and feedback was 180° reversed (i.e. decoupling of vision and action in two ways). We analyzed whether movement planning, timing, and trajectory variables differed between age groups. In accordance with our hypothesis, we observed no age-group effects for any movement planning, timing, or execution variables on the direct interaction task ($p<0.05$). However, in the CMI task, we observed that adolescents’ movement planning and timing was significantly shorter than that of children in the CMI task condition which required integration of cognitive information into the visually guided action. Subdividing the child group (8-10 & 11-12 yrs.), we further demonstrated that CMI maturation emerged mainly in the latter period. Our results quantify an important milestone during childhood for the development of CMI, i.e., the ability to decouple vision from action. CMI seems to develop strongly during late childhood, leading to better rule-based motor performance in early adolescence. Based on previous animal, human, and imaging studies, we propose this CMI development is mainly due to frontal lobe development and the strengthening of fronto-parietal networks, networks well known to heavily contribute to the successful integration of rule-based visually guided movement.

**Disclosures:** **M. Dalecki:** None. **D.J. Gorbet:** None. **L.E. Sergio:** None.

**Poster**

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** JSPS KAKENHI JP16H06566

**Title:** Rotated visual feedback of self-movement affects long-latency stretch reflex

**Authors: *S. ITO**, H. GOMI
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**Abstract:** Stretch reflexes, quick motor responses evoked by rapid extension of muscles, play a key role in postural control and movement correction. Previous studies have shown that long-latency stretch reflex in particular is flexibly modulated depending on various contexts including physical environments, movement intention or task goal. It is unclear, however, how the stretch reflex is affected by a discordance in motion between one's own limb and manipulated objects as in a situation where one uses complex tools. Here we tackled this issue by measuring the stretch reflex from wrist flexor muscle while introducing directional transformation into visual feedback of self-movements. In experiment 1, human participants repeated wrist flexion movement toward a visual target. In separated experimental blocks, locations of the target and direction of cursor movement were rotated around the center of a display (0, 45, 90, 135, 180 [deg]), while wrist movement was not changed. On the random trials, mechanical perturbation was applied on the wrist joint to evoke stretch reflex during the wrist flexion. We found significant reduction of the long-latency stretch reflex in the experimental blocks with larger visual rotation angles (> 45 [deg]). These results suggest that difference in movement direction between visual cursor and actual limb causes the suppression of stretch reflex. In experiment 2, participants performed a similar movement task, turning their heads toward left. Visual feedback was also rotated 90 degrees in a counterclockwise direction around the head axis so that the cursor motion was unchanged in eye-centered coordinate system. Stretch reflexes did not differ from control condition where direction of the head and visual feedback remained in front of the body. In other experimental block, visual feedback was additionally rotated 90 degrees in a clockwise direction on the center of visual field with participants' head turned. Though the direction of displayed cursor movement coincided with actual wrist movement in external coordinates, we found significant decrease in the stretch reflex. Those results indicate that observed reduction of the stretch reflex occurs depending on a body motion represented in eye-centered or head-centered coordinate system rather than external coordinate system. In conjunction with our previous observation of stretch reflex in a mirror-reversed visual feedback condition, our results suggest that somatomotor transformation for generating a long-latency stretch reflex is not solely coordinated within the somatosensory processing, but is established with a great contribution of visual information.

**Disclosures: S. Ito:** None. **H. Gomi:** None.

**Poster**

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** TRU Internal Research Fund

NSERC Discovery Grant

**Title:** Haptic feedback from stabilization of the hand on an underlying surface facilitates the initial development of visually-guided finger movements for reaching and grasping in 12-month-old human infants

**Authors: *J. M. KARL**, A. M. WILSON, C. WILSON, N. S. SHUBEAR
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**Abstract:** Traditional theories posit that development of the reach-to-grasp movement is dependent on visual guidance, proceeds in a proximal to distal fashion with reach movements of the upper arm maturing before grasp movements of the hand and digits, and is largely complete by 12 months of age. In contrast to this traditional view, recent research suggests that separate reach and grasp movements undergo significant developmental refinement based on somatosensory input long before they are integrated together under visual control. A precise description of how separate reach and grasp movements might transition from somatosensory to visual control during human development is currently lacking. The present study used the ethological task of reaching to grasp small ring-shaped pieces of cereal (Cheerios) to investigate the extent to which the reach and grasp depend on somatosensory versus visual guidance in twelve-month-old human infants. Twelve-month-old infants, sighted adults, and blindfolded adults reached to grasp Cheerios, which were located on either a flat table or on the top of a narrow pedestal. Their arm and hand movements were recorded from three different angles using time-synchronized high speed video cameras and analyzed offline using frame-by-frame video analysis. The reach and grasp movements of infants differed significantly from that of both sighted and blindfolded adults. When reaching to a Cheerio on a table, infants resembled blindfolded adults in that they almost always contacted the table with an open hand before they contacted the Cheerio; after table contact however, infants resembled sighted adults in that they used the tip of an appropriate grasping digit to establish first contact with the target. Despite unrestricted vision of the target and their own hand, infants were much less likely to use the tip of an appropriate grasping digit to establish first contact with the Cheerio when the Cheerio was located atop a narrow pedestal. The results suggest that the development of visual guidance of the reach-to-grasp movement might actually originate at the distal tip of the digit and be facilitated by initial haptic contact between the hand and an underlying table or surface. Contact with the underlying surface likely serves to: provide a haptic signal that the hand has reached the general target location, stabilize the endpoint of the reach at that location, and free up vision to attend to the interaction between the tips of the digits and the target.

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NSERC Discovery Grant

**Title:** Grasping 2D targets: The influence of shape and position on gaze and grasp accuracy

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**Abstract:** A stable grasp is one in which a grasp line connecting the index finger and thumb would bisect the target object's center of mass. When grasping either 2D or 3D stationary rectangles, our lab has seen this achieved by placing the index finger on the top edge, close to the horizontal center. However, when grasping horizontally translating targets with the right hand, we see a final index finger position that lands *to the left* of the target's horizontal center (Bulloch, Prime, & Marotta, 2015; Langridge & Marotta, 2016), regardless of direction. Individuals may be unconsciously adjusting their reaches and grasping ahead of a leftward moving target's center to account for the increased mechanical risk present when executing a grasp 'across the body' for a target moving away from the hand. This study investigated how target shape and position influence preferred grasp location. **Methods:** Participants executed right handed reach-to-grasp movements for stationary 2D shapes positioned on the left, right, or in the center of a computer screen. Shapes were either square (Fig. 1), or were missing part of the top and bottom edges, intended to force a choice between grasping the left or right side of the target (Fig. 2). **Results:** Final gaze and index placement was positioned further rightward when grasping 'complex' shapes compared to controls. Participants fixated on the right side of targets positioned on the left, the left side of targets presented on the right, and the center of central targets, regardless of shape. Index finger placement corresponded with gaze: A rightward bias was observed when grasping left and central targets, whereas a leftward bias was observed when grasping targets on the right. **Conclusions:** When reaching for 2D targets, individuals prefer to choose grasp locations that require the least amount of mechanical effort. Both the shape of the target and its position in relation to the reaching hand influences where gaze is directed and the preferred index finger placement when grasping.

Figure 1.

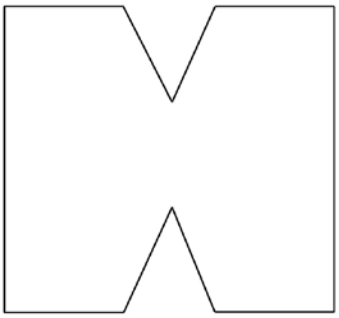

Figure 2.

**Disclosures:** **R.W. Langridge:** None. **J.J. Marotta:** None.

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** NSERC

CFI

ORF

**Title:** Potential models of allocentric coding for reaching in naturalistic visual scenes

**Authors: *P. ABEDI KHOOZANI**[1], M. KLINGHAMMER[2], P. R. SCHRATER[3], D. ENDRES[4], K. FIEHLER[2], G. BLOHM[1]
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**Abstract:** We use both allocentric and egocentric information when planning to reach to visual targets. Previous studies showed that contextual factors can modulate the integration of allocentric information, Klinghammer et al. 2015, 2016, 2017: e.g. when humans are exposed to similar scenes at two phases in a memory task, encoding for memorizing the scene configuration and decoding for reaching to a missing object, random shifts in objects of the scene lead to less contribution of allocentric information and higher variability in reaching compared to consistent object shifts. However, the principles of this integration and the impact of different parameters are not clear. Therefore, our aim is to examine potential principles for allocentric coding, using a modeling approach, to explain the reported data as well as make predictions for future experiments. We propose three models to estimate the position of a missing object using a

naturalistic scene. At the encoding phase the goal is to code and store the position of each object with respect to the other objects in working memory. The first two models perform this task by creating a cluster point and calculate the distance of objects from this cluster (first model is logistic Bayesian and the second model is generative Bayesian). The third model performs this task by creating Barycentric coordinates and encodes the position of the target object with respect to local clusters of objects. At the decoding phase, the goal is to infer the position of the missing object from the new scene and remembered information from encoding. In the first two models, this inference is done by combining the remembered egocentric cluster point, from encoding, and the new allocentric cluster point extracted from the new scene. The third model estimates the allocentric position of the missing object based on the new scene and then combines it with remembered egocentric position. All models reproduced the reported human data, but each model has different implications: Based on the first two models, the required computational and memory resources can be greatly decreased by creating a global cluster point, however, any misestimation in retrieving this cluster point, due to changes in the scene, can dramatically affect the final estimation (the first model in more efficient computationally while the second model Is more robust due to making less assumptions). In contrary, the third model uses a more redundant coding strategy (requiring more resources) by creating local clusters and therefore changes in the scene. Future experiments should be carried out to examine which of these strategies, if any, the brain might use.

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**Poster**

**495. Visually-Guided Reaching**

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**Topic:** D.09. Visual Sensory-motor Processing

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**Title:** Short-latency stimulus-locked responses on human upper limb muscles are preferentially evoked by low spatial frequency stimuli

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**Abstract:** To reach to a visible target, visual information ultimately has to be transformed into motor commands. Neural processing within numerous frontal and parietal cortical areas is likely important for such a sensorimotor transformation, with the outcome typically being relayed to the motor periphery via the corticospinal pathway. Recently, we have described stimulus-locked

responses (SLRs) on human limb muscles, which are brief bursts of muscle recruitment that evolve at time-locked latencies within ~100 ms of visual target onset, even if eventual reach is temporarily withheld or moves in the opposite direction. These observations have led us to hypothesize that SLRs arise from a fast visuomotor system mediated by the tecto-reticulo-spinal pathway, which runs in parallel to the corticospinal pathway. Very little is known about the nature of visual input that feeds into the fast visuomotor system.
To address this question, we examined whether the SLR is preferentially evoked by visual stimuli composed of either high-spatial frequency (HSF) information, which is primarily mediated by the parvocellular visual pathway, or low-spatial frequency (LSF) information, which is primarily mediated by the magnocellular visual pathway. Human subjects placed in a robotic exoskeleton generated planar arm movements toward visual stimuli to the right or left as surface electrodes recorded electromyographic (EMG) activity from the clavicular head of the right pectoralis major muscle. Visual stimuli consisted of perceptually contrast matched Gabor patches, spanning 0.26 to 4.44 cycles per degree of visual angle. LSF stimuli evoked the shortest-latency and largest magnitude SLR. Approximately 70 percent of participants presented with detectable SLRs at ~100 ms for LSF stimuli (SLR+). Further, SLR latency increased and SLR magnitude decreased for progressively higher spatial frequency stimuli. In the SLR+ participants, not all presented with detectable SLRs for the highest frequency stimuli, significant responses were only detected after 125 ms. Off-line analyses confirmed that these results were not due to concomitant changes in movement reaction time. Overall, our results demonstrate that the SLR, which represents the earliest wave of upper limb muscle recruitment in a visually-guided paradigm, is preferentially evoked by LSF stimuli carried by the magnocellular pathway.

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** CREST, Japan Science and Technology Agency

JSPS KAKENHI JP16H06566

**Title:** Temporal development of an interaction effect between internal motion and contour signals of drifting target on reaching adjustment

**Authors: *H. UEDA**, N. ABEKAWA, H. GOMI
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**Abstract:** When a moving object containing internal motion is seen in the visual periphery, the perceived position of the object is often distorted towards the direction of its internal motion. This phenomenon is known as motion-induced position shift (MIPS) and observed also in motor actions such as manual reaching and saccades. A recently proposed object-tracking model (Kwon et al., 2015) describes that MIPS is caused by a bidirectional coupling between position and motion perception. In particular, at high positional uncertainty (e.g., in peripheral vision), most of the retinal motion signal including internal pattern motion is mistakenly attributed to the object's global motion/position, and vice versa. Although many evidence of MIPS has been found, most studies so far have ceased to verify under what conditions MIPS occurs and almost no study has been focusing on the temporal development of MIPS. The present study, therefore, aimed to examine an open question that, in what time course, such MIPS (or integration of object's internal and external motions) occurs.
In the experiment, the stimulus of the curveball illusion (Shapiro et al., 2010), which deviates the perceived trajectory of a moving visual target from its actual trajectory towards the direction of internal motion, was adopted as a target stimuli, in which positional uncertainty levels were controlled by the aperture boundary: soft, moderate, or hard. In each trial, participants started forward reaching to the target stimuli which initially located at 25 cm away from the start position. Shortly after the reaching initiation, the target either moved 5 cm to the left or right or stayed the initial position accompanied by the onset of internal motion. All the combinations of external and internal motion directions (rightward, leftward, and no motion), except for incongruent directions, were tested. Participants were required to make online reaching adjustment in response to the target motion.
The results showed that the reaching adjustment started approximately 190 ms after the external/internal motion onset in all the motion conditions, even in the condition of internal motion only. The early phase of the reaching adjustment (< 225 ms) was not affected by the contour type. The late phase of the adjustment (> 250 ms), on the other hand, was greatly affected. These results suggest that MIPS is also observed in the reaching adjustment, but is slowly developed, compared to the direct effect of visual motion on the reaching adjustment. That is, the adjustment would be initiated prior to the integration of motion and position information, and effect of integration on the motor response would appear after a certain period of time.

**Disclosures:** **H. Ueda:** None. **N. Abekawa:** None. **H. Gomi:** None.

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**Topic:** D.09. Visual Sensory-motor Processing

**Support:** JSPS KAKENHI JP16H06566

**Title:** Modulation difference in visuomotor responses in implicit and explicit motor tasks depending on postural stability

**Authors: *N. ABEKAWA**, H. GOMI
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**Abstract:** In our daily life, we reach for target objects accurately under various postural environments. If body posture is not stable, we should make online corrections of reaching rapidly to compensate for body motion. Recent studies have shown that a large-field visual motion applied during reaching induces rapid and unintentional manual following response (MFR) in the direction of visual motion (Gomi, 2008). Considering that retinal motion occurs when our body moves, the visuomotor system can use visual motion signals arising from body movements to rapidly adjust reaching against unpredictable body motion. This functional view regarding the MFR can raise a fundamental question of whether the brain optimally modulates the implicit visuomotor response according to postural environments. Here, we tested this issue by examining the effect of postural condition (unstable or stable) on the MFR. Standing participants made reaching movements to a visual target on a vertical screen. On the random trials, large-field vertical gratings (size: 80 [hor.] x 66 [ver.] deg., Fs: 0.1 c/d) started to move rightward or leftward (velocity: 100 d/s) just after the initiation of reaching. Participants performed reaching under the two different postural conditions. In the UNSTABLE condition, participants were standing on the motor-driven platform with viewing static gratings, and were asked to maintain their posture during every trial interval (for approx. 5 sec.) against the instability induced by platform motion. In the STABLE condition, they were standing on the wood box, and there was no postural disturbance. Note that between both conditions, body posture was identical during the reaching (i.e. motor platform did not move during the reaching). We quantified the amplitude of the MFR implicitly induced by visual motion, and found that the MFR was significantly larger for the UNSTABLE than for the STABLE. In the follow-up experiment, participants performed the choice-reaction task where they pressed the right or left button as fast as possible according to the direction of visual motion. There was no significant reduction of reaction time for the UNSTABLE compared to for the STABLE. This would rule out the explanation that the change in the MFR results from postural condition affecting early visual processing commonly used in the implicit and explicit visuomotor tasks. Rather, our data suggest that the visuomotor transformation specific for the MFR is flexibly modulated by external environments according to the postural stability. In unstable environments, the brain would rely on implicit visuomotor controller more in order to effectively adjust reaching movements.

**Disclosures:** **N. Abekawa:** None. **H. Gomi:** None.

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**Topic:** D.09. Visual Sensory-motor Processing

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Fonds voor Wetenschappelijk Onderzoek

**Title:** Multi-electrode recordings in the macaque frontal cortex reveal common processing of eye-, arm- and hand movements

**Authors: *T. DECRAMER**[1], E. PREMEREUR[2], T. THEYS[3], P. JANSSEN[2]
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**Abstract:** Human observers always fixate certain landmark positions in a visual scene in which objects have to be grasped and moved to a different location, and the grasp site on the object is invariably fixated prior to grasping. However, the neural basis of eye-hand coordination in object manipulation is not well understood. Previous studies have shown that parietal regions such as MIP, LIP and AIP, which are heavily interconnected with frontal areas, may play a pivotal role. Frontal areas are involved in controlling different effectors such as the eye, arm and hand, but it is not clear how these different areas interact during naturalistic behavior involving eye, reach and grasping movements.
Two monkeys were trained in a sequential saccade-reach-grasp task, in which the animals had to first fixate a spot on a display, after which an object was illuminated in peripheral vision. After a variable delay, the animals had to make a saccadic eye movement to the illuminated object, and after a second delay, the animals were instructed to reach towards, grasp and pull the object. Both animals were implanted with a chronic 96-channel microdrive (Gray Matter Research) with individually-movable electrodes above frontal cortex, allowing access to primary motor cortex, dorsal premotor cortex, ventral premotor cortex (F5a, F5p), Frontal Eye Fields and area 45B. We recorded in 80 sessions during 4 months with over 1500 recording sites in each monkey. Electrode position was confirmed by repeated CT-MRI co-registration in which individual electrodes could be visualised.
We did not observe a clear separation of visual-, saccade-, reach- and grasp-related activity across frontal cortex. In contrast, we observed very similar response profiles in all frontal areas: an initial visual response to light onset, then a sustained increase in neural activity after saccade onset followed by an additional increase in activity in the epoch before the hand started moving towards the object. This cumulative effect of visual-, saccade-, reach- and grasp-related responses was present across all recording channels, from primary motor to the most anterior

parts of ventral premotor cortex. These results suggest that frontal areas work in concert during a saccade-reach-grasp task that mimics natural prehension behavior.

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Fonds voor Wetenschappelijk Onderzoek

**Title:** Multi-electrode recordings in the macaque parietal cortex reveal common processing of eye-, arm- and hand movements

**Authors: *P. JANSSEN**, E. PREMEREUR
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**Abstract:** Hand actions are usually performed in coordination with eye movements. For example, the grasp site on an object is invariably fixated prior to grasping. However, the neural basis of eye-hand coordination in object manipulation is not well understood. Previous studies have shown that parietal regions such as MIP, LIP and AIP may play a pivotal role. The latter areas are involved in controlling different effectors such as the eye, arm and hand, but it is not clear how these different areas interact during naturalistic behavior involving eye, reach and grasping movements. Two monkeys were trained in a sequential saccade-reach-grasp task, in which the animals initiated a trial by fixating a spot on a display, which was followed by the illumination of an object in peripheral vision. After a variable delay, the fixation spot dimmed, indicating to the animals to make a saccadic eye movement to the illuminated object. A second go-cue instructed the animals to reach towards, grasp and pull the object. Both animals were implanted with a chronic 96-channel microdrive (Gray Matter Research) with individually-movable electrodes above parietal cortex, allowing access to AIP, MIP, LIP, area 5 and PFG. We recorded in 171 sessions (monkey S: 87; 4187 recording sites, monkey O: 84 sessions; 4544 recording sites), and the electrode position was confirmed by repeated CT-MRI co-registration in which individual electrodes could be visualized. We found significant task-related multi-unit activity in 1460 sites (monkey O: 798 sites, monkey S: 662). A minority of these recording sites was responsive during object illumination (monkey O: 293 sites, monkey S: 167), and these recording sites were typically located more anteriorly in the IPS. On the majority of channels, however, we obtained an initial sustained increase in neural activity after saccade onset followed

by an additional increase in activity in the epoch before the hand started moving towards the object. We did not observe a clear separation of saccade-, reach- and grasp-related activity across parietal cortex. In contrast, we observed very similar response profiles in all parietal areas. These results suggest that parietal areas work in concert during a saccade-reach-grasp task that mimics natural prehension behavior.

**Disclosures: P. Janssen:** None. **E. Premereur:** None.

**Poster**

**496. Cortical Planning and Execution: Behavior**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 496.01/GG16

**Topic:** E.04. Voluntary Movements

**Title:** Development of locomotor skills in children

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**Abstract:** The study of neurological control mechanisms underlying movement maturation is important for the understanding of how motor skills are acquired during early childhood and the identification of motor milestones. Maturation of locomotor skills in typically-developing (TD) children was studied in the framework of the referent configuration (RC) hypothesis, an extension of equilibrium-point theory. Identification of mature patterns would be associated with the presence of periods of minimal activity in multiple muscles of the body when the actual configuration (AC) of the body coincides with the referent one (RC) during rhythmical movement. The objective of the study was to determine whether locomotor maturation was associated with the presence of EMG minima in 3 locomotor tasks of increasing complexity (walking, jumping, jumping forward). **Methods:** Ten TD children (aged: 3.9±0.9 yr) and 10 adults (aged: 21.7±1.3 yr) were recruited after signing informed consent forms approved by the local ethics committee. Children underwent a clinical evaluation of gross movement performance (Test of Gross Motor Development-Gross Motor Quotient, GMQ). Kinematics (12-camera Vicon 512 system, 24 markers on trunk and legs) and EMG from 5 muscles on each leg (Wave Wireless EMG) were recorded while subjects performed 3 locomotor tasks: walking (W), vertical jumping (VJ) and jumping forward (JF). EMG minima were identified across muscles of one (W) or both (VJ, JF) legs. The number of minima and the location at which they occurred in the leg movement cycle (measured by the ankle marker) for each task were determined. **Results:** GMQs ranged from 115-136 out of 160 (mean 121.9±6.5). For the 3 tasks, children tended to have fewer EMG minima per cycle (W: 0.8±0.3, VJ: 0.4±0.2, JF: 0.7±0.3) compared to young

adults (W: 1.0±0.0, VJ: 0.9±0.2, JF: 0.9±0.1). The percentage of the leg movement cycle at which the minima occurred differed between groups. Less mature children had no or fewer minima. Minima, when present occurred more frequently between 20-29% (W), 40-59% (VJ) and 50-69% (JF) compared to young adults (W: 60-70%, VJ: 50-70%, and JF: 30-50%). The number of EMG minima during the VJ task was correlated with GMQ ($r=0.71$, $p=0.03$). **Conclusions:** Less mature children had fewer minima that occurred in different locations compared to adults, while EMG minima in children with more mature movement patterns were similar to those in young adults. EMG minima may be indicators of locomotor maturation defined as the specification of an RC by the nervous system. Understanding the mechanisms underlying locomotor maturation in young children can help identify developmental disorders and delays.

**Disclosures: M.F. Levin:** None. **D. Chan-Viquez:** None. **N.A. Turpin:** None. **A. Lamontagne:** None. **A.G. Feldman:** None.

**Poster**

**496. Cortical Planning and Execution: Behavior**

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**Topic:** E.04. Voluntary Movements

**Support:** German Research Foundation (DFG) ZH 542/1-1

Natural Sciences and Engineering Research Council of Canada (NSERC) 121473-2012 RGPIN

Heart and Stroke Foundation of Canada (HSFC)

**Title:** Referent control of body orientation in the gravitational field: The role of the vestibulospinal system

**Authors:** *L. ZHANG[1], ***L. ZHANG**[1], *L. ZHANG[2], J. DAVOT[1,2,3], A. MULLICK[2,4], D. BARTHELEMY[2,5], M. F. LEVIN[2,4], A. G. FELDMAN[1,2]
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**Abstract:** Our postures and movements are oriented with respect to the direction of gravity. Body orientation changes when we lean forward from quiet standing position. The role of the vestibulospinal system in this process was investigated by assuming that this system should increase the spatial thresholds of anti-gravitational ankle muscles to let the gravitational torque

lean the body forward thus transferring body balance and stability to a new posture. Eight healthy subjects aged 19-40 yrs. old participated. Galvanic vestibular stimulation (GVS) was applied to compare the vestibulospinal influences during quiet standing, after intentional forward body leaning and after returning to quiet standing. Binaural stimulation (step impulse of 2mA current, duration 0.4s) was applied with the anodal electrode placed over the right mastoid process, after subjects turned their head to the left and closed their eyes at each position tested. Medium-latency EMG responses (MLRs; latency about 80-100ms) to GVS were recorded in ankle muscles (tibialis anterior and soleus of both legs) by post-stimulus averaging over 20 trials and normalized to the pre-stimulus EMG level. Compared with quiet standing, soleus MLRs were significantly reduced (by about 45%, paired t-test, $p=0.022$) at the position of forward leaning despite a substantial increase in the EMG levels in soleus muscles at this position. There was no change in tibialis anterior MLRs (paired t-test, $p>0.05$). Thus, during forward leaning, vestibulospinal facilitation of motoneurons of anti-gravitational ankle muscles was reduced. As a consequence, the EMG activity of these muscles initially diminished and then increased with reaching the final position of the forward leaning at which the increasing gravitational torque was balanced. Results support the prediction that to lean the body, the system changes the referent body orientation by shifting the spatial thresholds at which muscles of the body begin to be activated. Monotonic change in the body orientation gives rise to the observable non-monotonic EMG pattern without pre-programming. In contrast, direct specification of the EMG pattern without resetting the spatial thresholds for muscle activation would evoke resistance of posture stabilizing reflexes, preventing body leaning. This study advances the understanding of the role of the vestibulospinal system in the control of posture and movement by identifying a major control variable, the referent body orientation, underlying such control without direct pre-programming of motor commands to muscles and kinematics.

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**Poster**

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**Topic:** E.04. Voluntary Movements

**Support:** NSERC, Canada

HSFC, Canada

Canada Research Chair in Motor Control and Rehabilitation (MFL)

**Title:** Referent control of the orientation of posture and movement in the gravitational field

**Authors: *A. G. FELDMAN**[1,2], A. A. MULLICK[3], N. A. TURPIN[1], S.-C. HSU[4], S. K. SUBRAMANIAN[5], M. F. LEVIN[3]
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**Abstract:** This study addresses the question of how posture and movement are oriented with respect to the direction of gravity. It is suggested that neural control levels coordinate spatial thresholds at which multiple muscles begin to be activated in order to specify a referent body orientation (RO) at which muscle activity is minimized. Under the influence of gravity, the body is deflected from the RO to an actual orientation (AO) until the emerging muscle activity and forces begin to balance gravitational forces and maintain body stability. Postural corrections are produced by changing the RO, whereas the changes in muscle activity , forces and kinematics emerge, without pre-programming, due to deviation of the AO from RO. We tested several predictions of the hypothesis. (1) Dduring quiet standing on differently tilted surfaces, the same RO and thus AO can be maintained by adjusting activation thresholds of ankle muscles according to the tilt; (2) Intentional forward leaning of the body results from respective monotonic ramp-and-hold shifts in the RO. (3) Rhythmic oscillation of the RO about the ankle joints during standing results in body swaying; thereby at certain sway phases the AO and RO may transiently overlap, resulting in minima in the activity of multiple muscles across the body. EMG kinematic patterns in the 3 respective tasks were recorded and explained based on the RO concept that implies that these patterns are caused by referent control without being pre-programmed. In addition, as predicted, we confirmed the occurrence of minima in multiple muscles across the body at different body configurations during swaying. The role of the vestibulo- and corticospinal systems in the control of the body orientation in the gravity field is considered based on the notion of referent control of posture and movement.

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**Poster**

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**Topic:** E.04. Voluntary Movements

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Fulton Undergraduate Research Initiative (ASU)

Grand Challenge Scholars Program (ASU)

**Title:** Experts use the brainstem more for movement than non-experts: Evidence from startle-evoked-movement during typing

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**Abstract:** Recent evidence suggests that the brainstem is utilized more heavily following intense training. Bilateral motor cortex lesions do not disrupt the ability of rats to perform highly trained reaching (Kawai et a. 2015) - highlighting the importance of subcortical structures following learning. While provocative, this study was completed in rats and translation to humans is unclear. Startle-evoked-movement (SEM or startReact) represents a non-invasive way to evaluate the use of the brainstem (specifically the reticulospinal tract). We have previously demonstrated that SEM can detect the shift from cortical to brainstem usage following intensive training of finger abduction (Kirkpatrick et. al. 2017). Our objective here was to evaluate differences in brainstem usage between expert and non-experts. We hypothesized that the brainstem would be utilized more heavily in experts (showcased by the presence of an SEM in all fingers). We evaluated 8 expert (86.5 ± 12.9 WPM) and 8 non-expert typists (40.25 ± 14.6 WPM) with right handed dominance. The subject's right hand rested on the j, k, l, semi-colon, and space keys of a keyboard. A soft acoustic stimuli (80dB), informed the subject to prepare task execution. A go cue of either 80dB or 113dB was delivered 2-3 seconds later and directed them to press a specified key. The 113dB stimulus was intended to evoke a SEM. Keystroke and EMG data are collected. Analysis of the keystroke data revealed that SEM was present in all fingers of expert typists but none of the fingers of non-experts. In experts, SCM+ trials were faster than SCM- trials for the thumb ($\Delta$=0.024s; P=0.003), index ($\Delta$=0.029s; P=0), middle ($\Delta$=0.014s; P=0.04), ring ($\Delta$=0.029s; P=0.002), and little ($\Delta$=0.029s; P=0). There was no difference for any of the fingers in the non-expert population: thumb ($\Delta$=0.005s; P=0.618), index ($\Delta$ = -0.004s; P=0.677), middle ($\Delta$=-0.001; P=0.823), ring ($\Delta$=-0.006s; P=0.37), and little ($\Delta$=0.018; P=0.054). Importantly, there was no difference in the probability of evoking a startle between the populations. We conclude that experts utilize the brainstem to execute highly trained tasks indicating that the result from rats pertains to humans as well. Our results emphasize the importance of task familiarity towards an individual's ability to plan the execution of movements in subcortically.

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**Topic:** E.04. Voluntary Movements

**Support:** R00 HD073240

**Title:** Does startle enhance unrestricted, 2D reaching movement in stroke survivors?

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**Abstract:** Seventy-Five percent of stroke survivors have upper extremity deficits after acute stroke (Lawrence et al, 2001) which cause difficulty in essential movements like reaching and grasp. Recent work (Honeycutt & Perreault, 2012) has shown that startle can enhance stroke survivors' movements suggesting that startle can be used as a therapy tool. However, these studies evaluated single joint movements; therefore, it is unknown if startle will enhance movements when the arm is unrestricted allowing the full expression of abnormal muscle synergies and spasticity to affect movement quality. The objective of this study was to evaluate startle-evoked-movement during unrestricted, two dimensional reaching tasks. We hypothesized that startle would 1) decrease onset latency of muscle activity, 2) decrease movement reaction time and 3) increase the maximum speed of movement in stroke survivors. Moreover, we hypothesized that individuals who were not able to reach the targets would see increased movement distance.

Four eligible stroke subjects (Fugl-Meyer's ranging: 20 - 55 and Modified Ashworth scores ranging: 0 - 3) and two control subjects participated. Subjects reached to 3 different targets: mostly elbow, mostly shoulder, and both elbow and shoulder targets. Subjects were instructed to plan their movements and move from a home position to one of the targets following an auditory "GO" cue. "GO" cues were randomly replaced by a loud startling acoustic stimulus. EMG was collected in brachioradialis, biceps, triceps, pectoral, anterior and posterior deltoid muscles.

We found that startle decreased onset latencies of all muscles ($\Delta = 143.0 \pm 90.2$ ms) and decreased the reaction time ($\Delta = 139.2 \pm 113.0$ ms) in all subjects. Moreover, startle increased the maximum speed of the movement ($\Delta = 9.9 \pm 5.8$ cm/s). The most severely impaired individual (Fugl-Meyer = 20, Modified Ashworth = 3) saw the most dramatic enhancement of movement. Specifically, muscle onset latency decreased by $\Delta = 264.1 \pm 21.7$ ms. Furthermore, this individual only had quantifiable EMG activity in 37.3% of the trials during voluntary movement and 98.6% of the trials during startle. In addition, startle increased the movement distance of this individual ($\Delta = 2.8 \pm 0.3$ cm).

In conclusion, startle was able to enhance the movement of stroke survivors even in unrestricted

workspace. Further, the most significant improvements were seen in the most severely impaired individual who had high spasticity. This indicates that startle has the potential to play a role in therapy. Future work should evaluate how different levels of impairment and spasticity would affect the enhancements in stroke survivors.

**Disclosures: M. Rahimi:** None. **C.F. Honeycutt:** None.

**Poster**

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Fulton Undergraduate Research Initiative (ASU)

**Title:** Startle is able to evoke nearly identical movements in unrestricted, two dimensional reaching space

**Authors: *M. R. OSSANNA**, S. Y. SCHAEFER, C. F. HONEYCUTT
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**Abstract:** Startle-evoked movement—or the ability of startle to involuntarily release planned movement—has recently become a fixture in the literature due to its robust nature across numerous populations (i.e. stroke, Parkinson's) and joints (i.e. wrist, elbow, ankle). In addition, SEM has been shown to enhance single joint elbow movements and whole hand grasping in stroke survivors (Honeycutt et al, 2014, 2012). Still, almost all work to date has focused on single joint tasks while other joints were restricted. Indeed, others have often cited that SEMs were less precise than voluntary movements (Carlsen et al, 2004b) or exhibited differences in movement kinematics (Maslovat et al, 2011). Therefore SEM's ability to elicit multi joint movements of the whole arm is unclear. The objective of this study was to evaluate the ability of SEM to evoke unrestricted, two-dimensional movement. We hypothesized that SEM would be readily accessible across all directions even though we expected SEM movements to be less precise.

Ten right-handed subjects performed a reaching task to five targets that were equally spaced in a semi-circle to create a two-dimensional workspace. Target placement was chosen based on where arm stability is maximized (Hu et al, 2012). Subjects reached to each target following a sequence of two non-startling acoustic stimuli (60dB) cues: "Get Ready" and "Go". A loud acoustic stimuli (113dB) was randomly substituted for the "Go" cue with the intention of eliciting a SEM. Muscle activity during the performed movement was recorded using EMG for

bicep, triceps lateral, brachioradialus, pectoral, anterior and posterior deltoids. Movement time, acceleration, and position were also recorded during each reaching task.
We found that SEM was evoked in all five target directions as demonstrated by faster muscle onset latencies and movement start times. Muscle onset latency averaged across all 6 muscles and all targets had a delta value of 36.07ms ± 11.08 between SEM and voluntary movements. For movement start time, the average delta value between SEM and voluntary movements across all targets was 39.028 ms± 6.42. Interestingly, no differences were reported between voluntary and SEM trials in movement kinematics (i.e. total movement time, movement start time, linear deviation, average velocity, time to peak velocity) (all $p>0.05$). This result indicates that SEM can evoke functionally relevant movements. Our results represent the first step towards validating SEM as a potential therapy tool following stroke.

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**Topic:** E.04. Voluntary Movements

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**Title:** Generalization of complex motor skills: the transfer of dance movement sequences from trained to untrained contexts

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**Abstract:** Motor generalization refers to the ability to transfer learning from a trained context to an untrained context. Generalization of motor adaptation (e.g., induced by perturbing arm reaching movements with robotic manipulandums) has been widely studied through the variation of movement speed and extent (Goodbody and Wolpert, 1998; Mattar and Ostry, 2010; Joiner et al. 2011), configurations (Shadmehr and Mussa-Ivaldi, 1994; Shadmehr and Moussavi, 2000; Malfait et al. 2002), effectors (Criscimagna-Hemminger et al. 2003; Malfait and Ostry, 2004; Taylor et al. 2011; Joiner et al. 2013), and directions (Donchin et al. 2003; Thoroughman and Taylor, 2005; Hwang et al. 2006; Fernandes et al. 2012). These studies, however, investigated the transfer of motor learning using confined, simple movements. In the current study, we examined motor generalization using more complex motor skills. Specifically, we observed dancers' ability to transfer learning of an intricate movement sequence from a rehearsed to an

unrehearsed spatial orientation. This task is familiar to dancers as they are often required to learn movement sequences in a studio and later perform them on a stage with different spatial constraints given little, if any, practice. In our study, three dancers performed a movement sequence in three different spatial orientations: 1) a rectangular space (7.5 m by 5 m) serving as the trained orientation, 2) an untrained rectangular space with different dimensions (5 m by 7.5 m), and 3) an untrained circular movement pattern (radius of 2.5 m). While dancers performed the movement sequence in each spatial orientation, we tracked the position of the dancer using motion capture (OptiTrack). With these data we were able to 1) quantify the position of the dancers throughout the movement sequence in each spatial orientation and 2) quantify how these positions were adjusted in order to comply with the different spatial constraints in each orientation. Our results demonstrate that dancers have the ability to adjust their movements in accordance with varied spatial constraints. In addition, dancers were able to transform the movement sequence from a Cartesian coordinate system in the rectangular spaces to a polar coordinate system in the circular movement pattern. Our data suggest that the mechanisms underlying the motor generalization patterns studied in simple motor adaptation paradigms may also apply to more complex movement sequences.

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**Poster**

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**Title:** Presence and absence of prediction errors during action observation induce distinct motor contagions

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**Abstract:** Motor contagions are implicit effects induced in one's actions by watching of other's actions (Blakemore & Frith, 2004). The popular belief is that motor contagions such as automatic imitation, emulation, or outcome mimicry (Heyes, 2011) cause features (like kinematics, goal, outcome) of one's action to become similar to that of an observed action. On the other hand, Ikegami & Ganesh (2014) has recently reported a motor contagion that changes one's action but may not necessarily induce a similarity in it to the observed action. This contagion is induced not simply by observation, but by the presence of *prediction errors*- differences between actions one observes and those one predicts. To determine whether these two contagions are indeed distinct, here we examined the differences in the motor contagions induced by the observation of a same set of actions, in the presence and absence of prediction errors.

30 varsity baseball players took part in our study. In alternating sessions, the subjects observed a video of a baseball pitcher throwing a ball aimed for the upper right corner of a target strike zone (observation session), and threw a baseball themselves (throwing session) aimed for the center of the target. The throwing sessions were performed wearing a shutter goggle that shut when they released the ball from their hand, and prevented them from seeing where their throws hit the target. The subjects were divided into three groups (n=10 for each)- No prediction error (nPE), Prediction error (PE), and Control (CON) groups. The prediction error was manipulated by a difference of instructions between nPE and PE groups before each observation session. nPE group was correctly informed that "the pitcher is aiming for the upper right corner", which was expected to suppress prediction errors. PE group on the other hand was misinformed that "the pitcher is aiming for the center of the target" which was expected to generate prediction errors. CON group performed only the throwing sessions and not the observation sessions.

Even though only few words of instruction differed between the two groups, they showed completely different changes in motor performance. The throws by nPE group progressively deviated towards the upper right corner, similar to previously reported motor contagions. However, the throws by PE group progressively deviated towards the lower left corner, opposite to the direction of the observed throws. No deviation was observed in CON group. Our results clearly show the presence of two distinct types of motor contagions: one induced by features of the observed actions, and another by prediction errors related to the observed actions.

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**Poster**

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**Topic:** E.04. Voluntary Movements

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**Title:** Cognitive-motor integration is impaired in varsity athletes cleared for return to play and up to three months post concussion

**Authors: *A. PIERIAS**[1], J. HURTUBISE[2], C. HUGHES[3], A. MACPHERSON[3], L. E. SERGIO[4]
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**Abstract:** Our research examines cognitive-motor integration during eye-hand coordination. Such integration is often required when performing non-standard visuomotor tasks, where a rule is used to align the required motor output to the guiding visual information. We propose that cognitive-motor integration provides a simple, fast behavioural measure to track functional recovery following concussion. Previous cross-sectional research from our laboratory[1,2,3] has shown cognitive-motor integration declines in elite-level, university-level, child, and adolescent athletes who have a history of concussion (but were deemed recovered at the time of evaluation). To extend our research into concussion recovery, the current longitudinal study examines cognitive-motor integration (CMI) in young adult athletes at two time points during their return-to-play protocol following concussion. Participants were tested on two visuomotor transformation tasks using an ASUS tablet touch-sensitive computer attached to an external monitor or external touchpad. They made movements from a central target to one of four peripheral targets (up, down, left, right) by sliding their finger across the horizontally-placed touch-sensitive tablet displaying the targets. In condition one, participants viewed the targets on the touch-sensitive tablet. In condition two, participants viewed the targets on the upright, vertically oriented external monitor, with the cursor feedback 180$^{o}$ reversed so that the motion plane and cursor alignment were decoupled from guiding visual information (requiring CMI). We observed that, compared to their own baseline, these athletes continued to show performance impairments at the time they were cleared to return to their sport based on current return-to-play protocols[4]. Specifically, we found movement path length, movement time, and accuracy impairments relative to baseline during CMI, a skill that is often needed on the field of play. As well, some athletes showed deficits as long as three months following injury. These data suggest that the current return to play protocols do not fully capture functional abilities needed for many sports, and that their impairment may underlie an increased vulnerability to further concussion.
Ref: **1**. Hurtubise et al. 2016 **2**. Brown et al.2015, BMC SpSciMedRehab,Oct 19;7:25 **3**. Dalecki et al 2016 **4**. McCrea et al 2013 BrJSpMed

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**Poster**

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**Support:** NIH grant DC012245

**Title:** Engagement with a virtual clinician encourages gesture usage in speakers with aphasia

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**Abstract:** Aphasia is an acquired communication disorder that affects the ability to speak and understand spoken language. The use of gestures during speech is an important nonverbal means of communication that may facilitate speech production. We hypothesized that active engagement with a virtual clinician that produces natural gestures will support the emergence of more upper extremity and coordinated postural actions in patients with aphasia. Five speakers with aphasia (49 to 65 yrs) engaged in several communication tasks following instructions from a virtual clinician that: 1) did not use gestures, 2) exhibited gestures, and 3) again did not use gestures. Motion of the affected and unaffected thumb, index finger, wrist, shoulder and head of the patient were collected (Qualisys, Sweden) and analyzed off-line. Magnitude of upper extremity motion and trunk motion was determined by deriving the 95% confidence ellipsoid volume (CEV) of all of the gestures per condition for each subject. The Wilcoxon rank sum test was used to determine significant differences ($p<0.05$) between the CEV values according to trial condition. A taxonomy of gestures was created to identify whether each gesture was communicative or manipulative. Frequency of appearance of type of gesture was calculated. The number of gestures produced and the amount of time spent producing meaningful gestures was not significant between conditions. Magnitude of motion was significant between Pre-Gesture and Gesture conditions ($p\leq0.01$, $Z=-3.56$). Specifically, the non-affected index finger, thumb and wrist markers significantly differed ($p\leq0.01$, $Z=-3.10$) between Pre-Gesture and Gesture. No significance was found when comparing Pre-Gesture and Post Gesture conditions of the affected upper extremity ($p>0.05$, $Z=-1.50$). No significance was found between Pre-Gesture and Post-Gesture conditions. Results indicate that Individuals with aphasia did produce larger gestures after the clinician produced gestures with more forward trunk motion suggesting that they became more engaged with the virtual clinician over time. The results support the use of gestures with virtual clinicians for rehabilitation purposes.

**Disclosures: S.L. Snell:** None. **N. Martin:** None. **E.A. Keshner:** None.

**Poster**

**496. Cortical Planning and Execution: Behavior**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 496.11/GG26

**Topic:** E.04. Voluntary Movements

**Title:** Antiseptic Dorogov's Stimulator skin application effect on the animal's behavioral response

**Authors: *G. A. PIAVCHENKO**[1], R. BULTHUIS[2], L. BACHDASARIAN[2], V. I. NOZDRIN[1]
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**Abstract:** Antiseptic Dorogov's Stimulator 3 fraction (ASD) is a thermal processing of animal-origin tissues drug that is used for psoriasis, dermatitis and eczema treatment. Two doses of 5% drug (0,5 g/day and 4 g/day - groups 1 and 2 respectively) and drug base (Zn paste - control group) were applied on the shaved interscapular skin surface of Sprague Dawley male rats (age: 2 month, n=18) in a period of one week. Two hours after the last application the rats were recorded with the Laboras and Sonotrack research instruments (Metris, Netherlands) for identification of the behavioral responses. After intracardiac perfusion of the rats on frozen brain sections the c-Fos-positive cells were revealed by the avidin-biotin method using a 3,3'-diaminobenzidine detection (Santa Cruz, USA). The neuronal activation was observed in brain regions with reference to the Paxinos and Watson Rat Brain Stereotaxic Atlas (2013) on 13-15 section levels. Some activated cells in the motor cortex associative layer and a significant number of cells in the sensory cortex were observed in the control group. For the drug groups c-Fos positive neurons were found in the sensory cortex (same amount as in control group), and a significant activation of cells was registered in the motor, cingulate and piriform cortex and striatum. A high number of c-Fos-positive cells were observered in the caudate nucleus head, cingulate cortex and globus pallidus (drug group 1), and in the motor cortex and putamen (drug group 2). Although no local irritating action was mentioned, the average speed, the distance traveled and the number of behavioral acts increased, as well as the ultrasound vocalizations frequency decreased in according with the control groups in both drug groups. Finally it is concluded that ASD application on the skin causes c-Fos expression and an increase of motor activity, which may be interpreted as an indirect drug action on brain structures and behavior.

**Disclosures: G.A. Piavchenko:** None. **R. Bulthuis:** None. **L. Bachdasarian:** None. **V.I. Nozdrin:** None.

**Poster**

**496. Cortical Planning and Execution: Behavior**

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**Topic:** E.04. Voluntary Movements

**Support:** Grant NS078127

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Center for Sensorimotor Neural Engineering McGovern Institute

**Title:** Reasoning about errors in humans and nonhuman primates

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**Abstract:** Reasoning about errors is a key computational component of adaptive goal-directed behavior. An integral component of this computation is to dissociate internally- and externally-triggered sources of errors (e.g., “did I make a mistake, or were the instructions inaccurate?”). Here, we designed a novel behavioral task to investigate the computational principles of error monitoring in humans and monkeys. Subjects had to judge whether an interval demarcated by two flashes, one at the fixation point and one peripheral, was shorter or longer than an internal criterion, and report the decision by regulating a top-down inhibitory control to make either a prosaccade toward the second visual flash or an antisaccade away from it. The response contingencies were governed by two possible rules, either prosaccade (“Pro”) for “Short” and antisaccade (“Anti”) for “Long”, or vice versa, and the rules were switched during each behavioral session randomly after 10-26 trials. We tested subjects in two conditions. In the “External” condition, the color of the fixation point indicated the rule so that subjected had explicit information about the times of rule switch. In the “Internal” condition, the rule was not cued and subjects had to infer the times of rule switch from the pattern of feedbacks. To receive positive feedback, subjects had to correctly report the rule (which we solicited at the beginning of each trial) and make the correct response (Pro versus Anti). Subjects were able to perform the task in both External and Internal conditions and for both rules. As expected, performance was worse in the Internal condition, although an analysis of responses indicated that temporal judgements were similar across conditions, and the drop of performance was due to uncertainty about the rule. Subjective rule switches occurred after errors and increased systematically with

confidence about temporal judgment. Furthermore, the probability of switch increased with the number of errors indicating that subjects integrated evidence across trials in support of a potential rule switch. We were able to capture these results by an observer model that has structural knowledge about both internal sources of error related to timing, and externally-triggered sources of error due to the nonstationarity of the environment (rule changes). This indicates that monkeys, like humans, are capable of abstract rational reasoning about the various sources of errors. This opens the possibility of investigating the mechanisms of reasoning about errors at the level of single neurons.

**Disclosures: M. Sarafyazd:** None. **M. Jazayeri:** None.

**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

**Location:** Halls A-C

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**Program#/Poster#:** 497.01/GG28

**Topic:** E.04. Voluntary Movements

**Support:** NIH Grant R01NS082865

**Title:** Cortico-cortical functional connectivity between the primary motor and somatosensory cortical areas during grasp

**Authors: *S. LEE**[1,2], J. M. GOODMAN[1,2], S. J. BENSMAIA[1,2], N. G. HATSOPOULOS[1,2]
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**Abstract:** Primary motor (M1) and somatosensory (S1) cortical area of primates are known to be anatomically interconnected. However, very little is known how proprioceptive signaling in S1 interact with motor cortex to control naturalistic motor behavior such as grasping. By statistically analyzing the spatiotemporal interactions between the spikes with the local field potentials (LFPs) recorded across the areas, we tested the hypothesis M1 and S1 sites that shared similar somatotopic representations of the hand would exhibit stronger functional connections than pairs with dissimilar representations. Macaques were trained to grasp over 30 different objects and multi-camera Vicon motion capture system tracked the kinematics of reflective markers placed on the hand and arm of the monkey, from which we reconstructed the joint kinematics. High-density multielectrode arrays were used to sample single unit activity and LFPs from rostral and caudal motor cortex, area 3a, and area 2. Generalized linear models (GLM) were used to estimate the receptive/projection fields of each M1 and S1 neuron using various hand joint kinematics as predictors of firing rate of the neuron. We used a LASSO regularization technique which effectively isolated the most crucial joint kinematic features from the highly correlated joint movements of the hand. Having computed the somatotopy of neurons, we then inferred

functional connectivity by using the LFP signal from a site (as a proxy of the recorded neuron from that site) in one cortical area to predict the spiking response of neuron recorded in the other cortical area. By comparing model performance of the full model (GLM with LFP and joint kinematics covariates) and the reduced model (GLM with only joint kinematics covariates) on test data not used to build the models, we characterized the statistical significance of adding the LFP covariate in predicting the neural spiking. From a total of 72 pairs (38 similar and 34 dissimilar somatotopic pairs), 71% or similar somatotopic pairs showed significant model performance improvement whereas only 38% of dissimilar somatotopic pairs showed significant model performance improvement ($p<0.02$, t-test). We conclude that such functional connectivity structure maybe facilitates sensorimotor coordination of similar somatotopic representations.

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**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

**Location:** Halls A-C

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**Topic:** E.04. Voluntary Movements

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NIH Grant K99 NS101127

**Title:** Temporal dynamics of neural tuning to kinematics in primary motor cortex during reach-grasp-manipulation

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**Abstract:** Neurons in the primary motor cortex (M1) are known to represent kinematic features of upper extremity movement (Moran & Schwartz, J Neurophysiol, 1999). Though these representations commonly are considered time invariant, the improved linear encoding of movement fragments suggests a more complex temporospatial representation (Hatsopoulos et al., J Neurosci, 2007). We recently found that when subjects reach to different locations to grasp and manipulate various objects, neural activity evolves over time, being related more to location early and object later (Rouse AG & Schieber MH, J Neurosci, 2016). Here, we explore whether kinematics explain this neural modulation in a linear, time-invariant fashion, or whether kinematic representations encoded by M1 neurons show temporal dynamics.
Initially, we built encoding models in which each sorted unit's firing rate was predicted by the

position and velocity of six kinematic features: 1) the translation of the wrist in XYZ Cartesian space, and 2) the first three principal components of angular motion at 13 wrist and digit joints. These kinematic features were used to model firing rates at 20 evenly spaced time points across the entire movement time from movement onset to peripheral object contact (median movement time = 255 for monkey L, 235 ms for monkey X).
For 20 single time-point linear models at the appropriate times, the average R-squared for predicting firing rate was 0.30, whereas all-time linear models had an average R-squared of 0.23, only 78% of that explained by single time-point models. When single time-point models were used to predict the firing rates at other times > 100 ms earlier or later, however, these models had little predictive value (R-squared = 0 for a majority of sorted units).
We therefore built a mixture density neural network consisting of: i) multiple linear models, and ii) mixing coefficients that estimated the probability of each linear model for a given set of kinematics at each time point. The mixing of only two linear models predicted firing rates with an average R-squared of 0.29, explaining > 95% of the variance explained by the 20 single time-point models. ANOVA showed that 59% of the mixing coefficients' explained variance depended on time sample, 16% on location, and 25% on object, suggesting that neural encoding of kinematics shifts substantially with time rather than showing temporally invariant relationships to particular locations or objects. Our results highlight the temporal dynamics of the relationship between kinematics and M1 activity during naturalistic movements.

**Disclosures:** **A.G. Rouse:** None. **R.A. Jacobs:** None. **M.H. Schieber:** None.

**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

**Location:** Halls A-C

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**Topic:** E.04. Voluntary Movements

**Support:** Leibniz Association grant WGL SAW-2014-DPZ-1

**Title:** Reconfiguration of population responses between normal and reversed-vision reach planning in monkey sensorimotor cortex

**Authors: *H. GUO**[1,2], S. KUANG[3], A. GAIL[1,2,4]
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**Abstract:** Neurons in parietal reach region (PRR) of rhesus monkeys encode reach motor goals. A recent study disassociated physical goals from visual goals by using center-out reaches conducted under reversed vision. Statistics on the numbers of motor-goal neurons suggested

predominant but not exclusive encoding of physical goals in PRR (1). However, how neural population encoding during movement planning accounts for the perturbed feedback in motor control is still unclear. Under reversed vision, the spatial representation of a visual cue needs to be translated into an opposite-side physical goal. If monkeys by default initially plan a reach towards the visual cue location, then a spatial motor-goal remapping is required under reversed vision, equivalently to anti-reach planning. Intrinsic direction selectivity of each neuron could be preserved in this case, and remapping be achieved by selectively activating neurons with opposite selectivity. Alternatively, neurons might adapt their intrinsic direction selectivity to planning under reversed vision. In the first case we expect population activity during normal and reversed viewing to occupy the same subspace in neural state space; in the latter case we expect a re-configuration in state space. We tested our hypothesis in two monkeys conducting a memory guided reach task in both viewing contexts by analyzing neural dynamics in response to a motor-instructive spatial cue. Most neurons exhibited direction selectivity for the normal and the prism viewing context, ruling out recruitment of complementary subpopulations. But the subspace capturing the neural dynamics best in the normal-viewing captured only little variance of activity in reversed vision, which means the two subspaces are significantly misaligned. The result rejects the hypothesis that reversed reaching is achieved by simple remapping, which would happen in the same subspace. In contrast, pro and anti-reach planning is characterized by a much higher alignment of the corresponding subspaces, supporting the remapping model. Further, we show that task-related directional dimensions of the normal and reversed-viewing subspaces are close to orthogonal, while the time-related dimensions stay parallel, suggesting that misalignment between the normal and reversed subspace is endowed by the orthogonality of direction-related dimensions. We conclude that PRR exploits different neural dimensions for reach planning under reversed vision. Neural population responses are reconfigured to account for the perturbed feedback, instead of motor-goal encoding just being remapped as in spatial cognitive remapping tasks. (1) Kuang et al. Cerebral Cortex, 2016

**Disclosures:** **H. Guo:** None. **S. Kuang:** None. **A. Gail:** None.

**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

**Location:** Halls A-C

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**Topic:** E.04. Voluntary Movements

**Support:** ERC Parietalaction 323606

**Title:** Selectivity of posterior parietal cortex for observing action exemplars: A 100 actions fMRI study

**Authors: *S. FERRI**, G. A. ORBAN
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**Abstract:** Recent evidences showed that regions of human of posterior parietal cortex (PPC) are selective for observing exemplars of specific actions classes (Abdollahi et al 2013, Ferri et al 2015; Corbo and Orban 2017). The occipito-temporal (OT) regions activated in the same studies were very similar for all classes. However the selectivity for action classes of PPC regions was only proven using a restrict set of actions, typically 3x4 exemplars. To address this shortcoming we runs an fMRI action observation experiment using video clips of 100 different actions exemplars - like swimming, running, eating, measuring writing, manipulating an object, communicating with another person- covering all classes of the human repertoire, except those involving uro-genital apparatus, and recorded in a natural environment and involving only natural objects. 24 runs were recorded in three different fMRI sessions in right-handed, healthy subjects instructed to fixate a central target on the screen while passively viewing the videos. In each run we presented twice 25 actions exemplars plus fixation condition in 9s blocks (3TRs and 3 videos with the 3 actors). A single voxel analysis was performed on phAIP (419 voxels, Jastorff et al 2010), OTS (470 voxels) and MTG (417 voxels) ROIs (Ferri et al 2015) of the left hemisphere. After a first level analysis with 9 no-interest regressors (6 from realignment, session, motion and luminance), we contrasted the 100 actions with fixation to extract the corresponding fitted bold (in the last 2 TRs of a block) to obtain 2x2x3= 24 values for each of the 100 actions. These 24 values were used in a split analysis with 100 permutations to first determine the rank of the 100 actions and then the fitted bold corresponding to each rank. The average Bold-rank curve was fitted with a second-degree polynomial function to determine the rank corresponding to the 50 % of the maximum of BOLD response, as an index of selectivity.
The distribution of indices included significantly more small values (<40) in phAIP than in the OT ROIs in all three subjects analyzed (2x3 $\chi^2$ = 128.7, 135.1 and 145.3, all <0.001). These data show that phAIP voxels are activated by a smaller number of observed actions of the human repertoire than LOTC voxels, confirming the greater selectivity of the representation of observed actions at the PPC compared to the OT level.
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**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

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**Topic:** E.04. Voluntary Movements

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Istituto Italiano di Tecnologia

**Title:** Neuronal selectivity for observed hand actions in monkey's anterior intraparietal area

**Authors: *M. LANZILOTTO**[1], M. MARANESI[2], A. LIVI[1], C. G. FERRONI[1], L. FOGASSI[1], L. BONINI[1], G. A. ORBAN[1]
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**Abstract:** The ability to discriminate between observed actions is a fundamental aspect of social behavior in primates (Platonov and Orban Sci Rep 2016). It is known that visual information on observed action is processed in temporal brain regions and conveyed to premotor cortex by inferior parietal areas (Nelissen et al J Neurosci 2011). Among these, the anterior intraparietal area (AIP) is gaining increasing interest because its human homologue is specifically activated by the observation of manipulative actions (Ferri et al Hum Br Mapp 2015). However, despite the rich knowledge about the capacity of area AIP neurons to process objects features, a detailed description of their tuning to different manipulative actions is still lacking. To address this issue, we recorded single neuron activity from two macaque monkeys (MK1 and MK2) while they observed video portraying 7 different manipulative action exemplars (drag, drop, grasp, push, roll, rotate and squeeze) performed by two actors (male and female) on two objects of different colors (orange and magenta). Neurons were recorded from 4 linear silicon multi-electrode probes (32-Chs each one) chronically implanted in the right (MK1) and left (MK2) hemispheres, along the entire rostro-caudal extension of AIP. We found that about 20% of AIP neurons showed action selectivity (significant 7x2 repeated measures ANOVA). Although all actions were represented, fewer neurons preferred rotate and squeeze exemplars. Furthermore, in a control experiment carried out on MK2, the 7 actions were presented in 9 different positions within the visual field, one at the fixation point and the remaining 8 at 3° eccentricity. This experiment showed that about 30% of the tested neurons were action selective (significant 9x7x2 repeated measures ANOVA). Among these action selective neurons, 67% showed tuning for the relative position of the observed action in the visual field, whereas the remaining 33% were just action selective. These findings constitute the first single neuron evidence in macaque that area AIP, besides underlying visuomotor coding of object features, also plays a role in discriminating between observed manipulative actions exemplars, suggesting that it could constitute a crucial node in the cortical action observation network.

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**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

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Istituto Italiano di Tecnologia

**Title:** Anatomo-functional evidence on the role of pre-supplementary motor area F6 in the extended cortical grasping network

**Authors: *M. GERBELLA**[1], M. LANZILOTTO[2], M. MARANESI[1], A. LIVI[3], C. G. FERRONI[5], L. BONINI[4]
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**Abstract:** The macaque mesial premotor area F6 is an arm-related area involved in the specification of “whether” and “when” to perform an intended action, particularly in complex “cognitive” situations, but it has been recently proposed to constitute an additional node of the cortical grasping network (Lanzilotto et al. 2016). In this latter study, we recorded neural activity along the rostro-caudal extent of area F6 from two monkeys (Mk1 and Mk2) with chronic linear multielectrode probes during a reaching-grasping go/no-go task with three different objects as targets, to be grasped with different types of grip, in the light and in the dark. Many of the recorded neurons showed task-related visual and/or motor responses, and a set of them (26%) also exhibited visual and/or motor selectivity for the target object. To further support from an anatomical point of view the proposed involvement of area F6 in the cortical grasping network we performed an anatomical tracing study of the functionally characterized F6 sectors. To this purpose, at the end of the recordings the probes were removed and 2 neural tracers for each investigated hemisphere of Mk1 were injected at different anatomical positions within the functionally characterized region. We found that all the injections showed a common pattern of connections compatible with that reported in a previous study (Luppino et al. 1993). In the frontal lobe labeling was found in adjacent area F3, dorsal premotor areas F7 and F2, ventral premotor areas F5 and F4, prefrontal area 46 as well as in the cingulate motor cortex. In the parietal lobe, connections were observed with the intraparietal areas AIP and MIP as well as with the inferior and mesial parietal areas PFG, PG, V6A, PGm, and PEc. Additional prefrontal connections with area 8Ad were observed only after the more rostral injection. More interestingly, the stronger connectivity of the posterior/middle part of F6 with the hand-and-

mouth related ventral premotor areas F5 and F4, as well as with the grasping-related parietal areas PFG and AIP, fits well with its robust neuronal tuning to motor and visuomotor processing of objects relative to the more rostral part. In turn, the more rostral part of F6 showed stronger connectivity with visual and reaching/grasping-related parietal area V6A, reaching-related premotor area F7, and eye-related prefrontal areas 8Ad and 46d, suggesting its anatomo-functional involvement in the online control of reaching-grasping motor acts and their integration with eye movement. Altogether, these findings highlight the anatomo-functional correlations underlying the recently proposed contribution of area F6 to the extended cortical grasping network.

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**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

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**Topic:** E.04. Voluntary Movements

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ERC Grant WIRELESS 678307

**Title:** Anterior intraparietal (AIP) neurons encode actions and pantomimes from dynamic and static stimuli

**Authors: M. MARANESI**[1], M. LANZILOTTO[2], A. LIVI[2], C. G. FERRONI[2], M. ANDUJAR[2], *L. BONINI[2]
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**Abstract:** The processing of observed actions involves several parietal and frontal areas. Recent findings revealed that neurons of the anterior intraparietal area (AIP), in addition to their well-established role in the extraction of object affordances for hand-grip selection, can become active when monkeys observe videos of both grasping actions and of an isolated hand moving in the visual field (Pani et al J Cogn Neurosci 2014; Maeda et al J Cogn Neurosci 2015), suggesting that these neurons may constitute a first step in the cortical recognition of observed actions. However, action recognition may still be possible even if the available information is partial, e.g. when only the hand (without the object) is visible, or when the action is presented in a static image. To investigate this issue, we have compared macaque monkey's AIP single neuron activity during 1) the observation of dynamic videos and pantomimes of grasping actions and 2) the observation of a static image (single frame) taken from each video during the real (or

pantomimed) hand-target interaction phase. Recordings were carried out with linear multielectrode silicon probes, chronically implanted in area AIP of one monkey trained to keep fixation during the presentation of visual stimuli. Stimuli depicted a hand grasping a little sphere (with precision grip) or a big sphere (with power grip), and pantomimes of the same actions (with no object). We recorded 130 neurons. Among them, 89 showed a response to at least the static and/or dynamic stimuli and were therefore classified as task-related: most (85.4%) responded to dynamic stimuli, with half of them encoding static pictures as well (46.1%). A few neurons responded selectively to static stimuli (14.6%), whereas almost all task-related neurons discharged during the observation of both action and pantomime. In a few cases, they showed a differential activation depending on the grip type during both action and pantomime (i.e. the object did not seem to be essential): interestingly, these differences occurred more frequently with dynamic (22.4%) than static (6.3%) stimuli. Altogether, these findings revealed that a moving hand is generally sufficient to trigger the activity of AIP neurons, even if it is not directed to an object, and they also suggest that the neuronal response cannot be accounted for by object presentation. The observation that static hand-grasping stimuli (with or without the object) can trigger AIP neurons discharge is an important step for using static stimuli to better investigated AIP neural dynamics underlying visual processing of observed hands.

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**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

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**Topic:** E.04. Voluntary Movements

**Support:** European Union's Seventh Framework Program (FP7/2007-2013) n 600925

**Title:** A visual-to-motor gradient in AIP: An anatomo-functional study

**Authors: C. G. FERRONI**[1], M. GERBELLA[2,3], M. LANZILOTTO[1], M. MARANESI[2], A. LIVI[1], E. BORRA[1], L. FOGASSI[1], L. BONINI[1], *G. A. ORBAN[1]
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**Abstract:** Primates use vision to guide their actions in everyday life. In macaques, visually guided object grasping is known to rely especially on intraparietal area AIP, which contains various classes of motor and visuo-motor neurons. Indeed, its anatomical connections with caudal intraparietal (CIP) and posterior intraparietal (PIP) areas, sensitive to both structural and

positional stereo information on objects, makes it a crucial node of the parieto-frontal network underlying visuomotor transformation for object grasping. In addition, the strong link with the inferotemporal (IT) cortex renders AIP a core area of the parieto-frontal action observation network. MR-based studies suggested the existence of a visual-to-motor gradient in AIP (Janssen et al. 2015; Durand et al. 2009). In order to obtain further evidence for such a gradient we recorded neuronal activity from 2 hemispheres of 2 monkeys (Mk1 and Mk2) using linear multielectrode silicon probes, chronically implanted at different antero-posterior levels of the area. Monkeys were trained to perform a reaching-grasping go/no-go task with three different objects as targets, to be grasped with different types of grip, in the light and in the dark. In addition, they also observed the same task done by an experimenter. At the end of the recordings, probes were removed and 3 different neural tracers injected at different rostro-caudal positions of the functionally characterized region in the right hemisphere of Mk1. We found that all the injected sectors of AIP showed connections with adjacent inferior parietal areas, superior parietal area MIP, the hand region of SII, premotor area F5, and prefrontal area 46v, in line with a previous study (Borra et al. 2008). Further labeling was observed in the dorsal premotor area F2, in the cingulate motor cortex, and in mesial parietal areas PGm and V6A, likely due to injection sites that also involved adjacent areas PFG and PG. In IT and in the caudal intraparietal areas LIP, CIP, and PIP relatively strong labelling was found only after the most caudal injections, whereas these connections were very weak following rostral injections. This rostro-caudal connectivity pattern appears to match with the distribution of functional properties. Indeed, the caudal portion of the investigated region showed more visual responses and visuo-motor selectivity for the target object and observed actions relative to the most rostral ones. These data support the existence of a caudo-rostral visual-to-motor gradient within area AIP.

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**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

**Location:** Halls A-C

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**Topic:** E.04. Voluntary Movements

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**Title:** Barriers in the brain: Pragmatic representation of objects by single neurons of the cortical grasping network

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**Abstract:** Brain processing of objects around us involves visual areas as well as the parieto-frontal motor system. This latter extracts from the object visual image the various motor possibilities for interacting with it (object affordances). The visual-to-motor transformations underlying object affordance processing rely on a circuit encompassing the anterior intraparietal area AIP, the ventral premotor area F5 and the pre-supplementary motor area F6 (cortical grasping network). In everyday life, contextual and physical barriers can prevent an observer from interacting with objects, though leaving unchanged their visual image: how does single neuron activity in the cortical grasping network represents objects behind a barrier?
Here, we answered this question by recording single neurons activity from area AIP, F5 and F6 of 3 macaques while they performed a visuomotor reaching-grasping task with three different target objects, each graspable with a specific type of grip: a ring (hook-grip), a small cone (precision grip) and a big cone (power grip). Object presentation responses were tested 1) during Go trial, which instructed the monkey to reach and grasp the target, 2) during No-Go trial ("contextual barrier"), which instructed the monkey to stay still, as well as 3) in the presence of a transparent plastic screen interposed between monkey's hand and the target ("physical barrier"). We recorded a total of 781 neurons from the three areas. Besides single neuron responses, we also decoded the activity of the whole neuronal populations of each area by means of a pattern classifier. The results revealed several interesting differences among the investigated areas in terms of 1) percentage of visually responsive neurons (about 63% in AIP and 30% in both F5 and F6), 2) distribution of neural selectivity for the different objects and 3) most importantly, effect of barriers. Indeed, contextual and, even more, physical barriers reduced both the magnitude of activity and object selectivity of premotor areas, particularly area F5, where object classification accuracy based on population activity dropped down to near-chance levels. These findings reveal that premotor areas provide a pragmatic description of potential target objects, depending on the agent's intention and possibility to interact with them. In contrast, AIP neural responses showed greater invariance to both contextual and physical barriers, suggesting a more visual-based encoding of object features. These findings shed light on how physical and contextual barriers affect neural processing of observed objects in the cortical grasping network.

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**Poster**

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**Topic:** E.04. Voluntary Movements

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Katie Samson Foundation

**Title:** Object and grasp-type information in premotor and MI neurons during imitated actions

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**Abstract: Mirror neurons** (MN) located in ventral and dorsal premotor and primary motor cortices (PMv, PMd, MI, respectively) are thought to play an important role in understanding and imitating actions of others. These neurons are active both during performed and observed actions. The proposed mechanism through which MNs mediate action understanding and imitation hinges on similarity in activity patterns during similar observed and performed actions. So far, no experiment has tested these hypotheses directly.
Here we trained macaque monkeys to perform a cued reach-to-grasp task with various object and grasp options. In addition, experimenters performed the same actions with cues invisible to the monkeys and the animals had to repeat the movement in order to receive a reward. The addition of action imitation to the experiment ensured that the monkey paid attention to the experimenter's movements.
We estimated information about target object and grasp type present in neural activity of single neurons and ensembles during observed and performed actions by computing trial-by-trial decoding performance. We found that **information about observed actions** is indeed present in PM and MI neurons, however information **is not limited to MNs** (i.e. neurons with significant changes in firing rate for both action observation and execution). In fact, non-MNs and even neurons whose firing rate distributions are not significantly different between pre-movement and movement times have grasp and object information at levels comparable to MNs. We also found that observed movement information can only be decoded during a short time window at object contact. This suggests that information about the movement to be imitated is stored in short-term memory elsewhere until retrieved again during movement execution.
We employed spike train similarity space (SSIMS) projections of single unit and ensemble activity to compute task-relevant information at different time points. This analysis is sensitive to both differences in spike rate and spike patterns. In our ongoing research, we investigate under which conditions rates or precise timing dominate information transfer in motor cortex.
In summary, we developed a task ensuring the animal's attention during observed movements. We show that **information about observed movements is widespread across** the **PM and MI** population. Non-MNs carry information comparable to MNs, and even units classically considered 'unresponsive' are task-informative through firing pattern variations.

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**Poster**

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**Title:** Contribution of premotor and primary motor cortex to the execution of gross and fine reaching tasks in rats

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**Abstract:** Acquired brain injuries, such as stroke or traumatic brain injury, are often associated with persistent motor deficits. Following a lesion to motor cortex, reorganization occurs throughout the remaining brain regions, and is thought to underlie motor recovery. Unfortunately, the neurophysiological and neuroanatomical endpoints typically associated with reorganization do not directly monitor the relevance of these changes to specific motor behaviors. This study examined the neural activity associated with execution of rodent reaching movements on a ms by ms time scale. Specifically, we developed a novel rodent reaching task consisting of a ‘gross’ lever press that allows access for performing a ‘fine’ pellet retrieval. The ‘gross’ and ‘fine’ movements have similar limb trajectories but the pellet retrieval requires both finer control of the distal forepaw and increased sensorimotor integration for successful task completion. We trained 5 healthy, male, Long-Evans rats (*Rattus norvegicus*) to perform the task. Each animal was able to learn to successfully perform the task with baseline accuracies exceeding 50%. In each animal, two chronic, 16-channel microeclectrode arrays were implanted in motor cortex contralateral to the reaching forelimb, with one array implanted in the caudal forelimb area (rodent primary motor cortex or CFA) and a second implanted in the rostral forelimb area (rodent premotor cortex or RFA). By collecting multichannel recordings of multiunit spiking activity, we were able to systematically analyze of the neural correlates of each individual motor behavior across cortical areas and task conditions. Specifically, approximately 60% of channels with multi-unit spiking activity had statistically significant ($p<0.01$) changes in firing rate time locked to both the button press and pellet retrieval events. An additional 30% of

channels had significant firing rate changes time locked to the pellet retrieval but not the button press. Firing rate modulations were greater in amplitude during the pellet retrieval relative to the button press with an overrepresentation of channels modulated only during the button press within RFA relative to the total number of channels. These results add to the existing literature describing the importance of RFA, particularly in more complicated motor tasks involving fine control of the distal forepaw and increased demands for sensorimotor integration. Furthermore, this study helps to characterize the normal task-related activity of RFA and CFA respectively, establishing a baseline for future comparisons in injured animals.

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**Title:** Properties of mirror neurons in the dorsal premotor cortex of the macaque brain. Comparison with F5 mirror neurons

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**Abstract:** Neurophysiological studies have reported the existence of dorsal premotor cortex (PMd) neurons that discharge both when a monkey executes a conditioned task (moving a cursor to capture targets on a computer screen) and when the monkey observes the visual stimuli associated with the performance of the same task either replayed or executed by the experimenter. Although these neurons display motor and observation evoked neural activity as F5 and parietal mirror neurons (MirNs) do, it is still debatable whether PMd contains MirNs. This is mainly due to the lack of evidence on whether the observation of the interaction between

a biological effector and an object (the standard visual stimulus evoking the discharge of typical MirNs) would also be effective for triggering the discharge of these PMd neurons. Here, we investigated whether PMd contains neurons that respond during both the execution and observation of reaching-to-grasp actions performed by the experimenter and compared their properties to those of F5-MirNs in terms of timing, response selectivity and action representation.
We identified neurons in PMd of the macaque brain that respond during the execution and observation of reaching-to-grasp actions, thus fulfilling the criterion for being considered MirNs. Cross-correlation between the single neurons' responses in the two conditions revealed that both PMd- and F5-MirNs neurons fire earlier in execution than in observation. During observation, PMd contained as many action selective MirNs as F5 and this resulted in similar selectivity indexes in the two areas. During execution, more F5 than PMd-MirNs neurons were selective and this was reflected also on the higher selectivity indexes in F5 than in PMd. In both areas the grip selectivity tended to be higher in execution than in observation, and the onset of action selectivity occurred later in observation than in execution for the majority of the neurons. The matching between the execution and observation discharge of MirNs in the two cortical areas was evaluated both at the single neuron and the population levels and was low in the former and high in the latter case. Furthermore, representational similarity analysis revealed that encoding of actions in PMd and F5 is alike, during both observation and execution. Besides the many similarities shared by PMd and F5 MirNs we found that PMd is not only activated but also displayed action related information earlier than F5 during both conditions.
The existence of MirNs in PMd that are recruited earlier than the akin F5-MirNs dictates the need to revise not only the nodes of the MirN circuit but also the flow of information within it and inevitably the sub-served functions.

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**Topic:** E.04. Voluntary Movements

**Support:** NIH/ NICHD grant 1R01HD071978-01A

**Title:** Adaptation of grip forces to 3D printed surface textures

**Authors: *S. BILALOGLU**[1], C. TYMMS[3], E. P. GARDNER[2], P. RAGHAVAN[4]
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**Abstract:** Friction at the skin surface is an important aspect of haptic perception that is used to adapt the fingertip forces to the grip surface to prevent use of inadequate or excessive grip forces. Previous work on grip force adaptation has used non-parametric natural materials or a narrow range of artificial substances. The advent of high-resolution 3D printing technology provides the ability to fabricate arbitrary 3D shapes and textures of precise surface geometry to be used in tactile studies. Using high resolution stereolithography 3D printing and parametric modeling, we created nine different surface textures, where the texture elements ("textons") were truncated cones with 0.1, 0.3, or 0.5 mm diameters spaced 0.75 mm, 1.0mm, or 1.25mm apart. In previous studies, Tymms et al (2016) found that surfaces with small wavelengths and large textons are judged smoothest, and textures with large wavelengths and small textons are judged least smooth. In this study we measured changes in friction and grip force adaptation during precision grasp and lift using an instrumented grip device with 3D printed grasp surfaces. Ten healthy adult subjects grasped the instrument using bare hands or with a thin layer of plastic (Tegaderm) applied to the fingertips. Adaptation of fingertip forces was quantified using the peak grip force rate (PGFR), and the coefficient of friction (COF) of the surfaces was computed as the inverse of the slip ratio (grip force/load force at the moment of slip). When grasped with bare hands, surfaces with large wavelengths and small textons were perceived as rougher, and produced lower PGFR, and a significantly higher COF. Friction was negatively correlated with subjective smoothness estimates in which small wavelengths and large textons were rated smoothest. This study also confirms previous findings that the tegaderm changes COF between the fingers and the tactile surface, and impairs the efficiency of grip force adaptation to the spacing and texton size. Textures generated with different texton sizes and wavelengths using stereolithography 3D printing can be used to generate a variety of quantified frictional surfaces that can be used in studies of tactile roughness perception and in related neurological applications. Additionally, we note that covering the fingertips with the tegaderm membrane effectively impairs tactile discrimination and adaptation of grip forces.

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**Topic:** E.04. Voluntary Movements

**Title:** Level of arm motor impairment predicts sensory modalities that optimize learning with the Bimanual Arm Trainer in patients with severe stroke

**Authors: *A. TANG**[1], S. BILALOGLU[1], C. BAYONA[1], J. STONE[1], M. WILFRED[2], C. HUNG[3], A. YOUSEFI[1], P. RAGHAVAN[1]
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**Abstract:** Few options exist for training arm movements in patients with severe chronic hemiparetic stroke who have very little active range of motion in their affected arm. Coupled bimanual training can prime the ipsilateral motor cortex for subsequent training with the affected arm and has shown to promote greater improvement in arm function as compared to training with the affected arm alone. The purpose of this study was to test the extent to which motor learning can be enhanced using specific sensory stimuli during coupled bimanual arm training, and whether level of impairment predicts which sensory stimuli will optimize learning in the affected arm in a given patient. The Bimanual Arm Trainer (BAT, Mirrored Motion Works, Inc.) links the movements of the affected and unaffected arms to perform external and internal rotation at the shoulder, which is combined with auditory and visual stimuli to enhance movement provided by a customized video game. 15 subjects with chronic post-stroke hemiparesis were tested on the BAT for 30 minutes. Subjects completed 4 sets of 10 trials. Each trial consisted of 30 second bouts of shoulder movements performed alternatively with both arms (bimanually) or unimanually with the affected arm alone. Each set presented a different sensory condition for movement in a random order, consisting of: (1) rhythmic auditory stimuli, (2) visual stimuli, (3) both auditory and visual stimuli, and (4) no additional stimuli. Upper limb motor impairment was assessed using the Fugl-Meyer Scale and active range of motion on the BAT. The slope of the learning curve for trials with the affected arm was computed for movements under each of the 4 conditions. We found that as the level of motor impairment increased, the sensory modality that produced the highest learning curve changed: subjects with the lowest Fugl-Meyer scores and range of motion showed steeper learning curves with auditory stimuli, followed by no additional stimuli, then visual stimuli and finally, those with the highest Fugl-Meyer scores and range of motion in the cohort responded best to both auditory and visual stimuli. The results suggest that patients may have different thresholds for processing sensory information for motor learning across the various stages of recovery. Motor learning may be optimized by providing the appropriate sensory stimulus based on an individual's stage of recovery post stroke.

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**Poster**

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**Support:** R01HD071978

**Title:** Eye-hand coordination during reaching to grasp task in the real world

**Authors: *A. YOUSEFI**[1], S. BILALOGLU[2], J. STONE[3], A. TANG[5], J. R. RIZZO[4], Y. LU[6], P. RAGHAVAN[7]
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**Abstract:** Efficient grasp requires proper planning grounded on visual perception of object shape. In this study, we explore the relationship between gaze location, finger position, and hand shaping during reach-to-grasp for objects of various shapes. Seven neurologically intact subjects sat at a table and reached towards and grasped an object positioned at 75% of their arm's length for seven times. They repeated the task for nine different shapes while their gaze, hand, and fingers were tracked. Reach-to-grasp was divided into pre-reach, acceleration, deceleration, and grasp based on wrist velocity. The finger position on the objects was relatively consistent across the subjects. Gaze location on the object was predominantly above the center of mass, corresponding most closely with the final position of the index finger. During the first trial, subjects fixated on the object most in the acceleration phase, but there were fewer fixations of longer duration. In the practiced trials, they fixated on the object the most in the deceleration phase and showed a larger number of fixations. The gaze location was measured as the distance between the fixation point and the final finger position on the objects. From the time of eye-opening, across all shapes, the gaze-finger distance was consistently smallest for the index finger followed by the thumb, and it was the longest for the little finger. The gaze-finger-distance was significantly smaller on the practiced trials for all fingers compared to the first trial. Since gaze was primarily directed at the index finger, we focused on the gaze-index distance as a measure of eye-hand coordination. Hand shape was computed as the difference between the final position of the fingers and the real-time position during reach-to-grasp. On the first trial, object shape determined the initiation, termination and the pace of the hand shaping. For the convex shapes, hand shaping started immediately at pre-reach and ended at grasp, although the hand shape was achieved earliest for the planar rectangular shape. In contrast, for the concave shape, hand shape began to occur after a delay. Shape-specific differences were less prominent in the practiced

trials as hand shaping started early reach and shaped fast as for the rectangular shape on the first trial. The results suggest that simultaneous examination of gaze patterns and finger positions can disclose eye-hand coordination which enables us to improve treatment strategies for patients who may have impaired eye or hand function. This information can serve as a benchmark for the assessment of eye-hand coordination in neurologically impaired patients such as stroke.

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**Poster**

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**Topic:** E.04. Voluntary Movements

**Title:** Enhanced upper limb motor control with intramuscular hyaluronidase injections in pediatric patients with cerebral injury

**Authors: *V. A. TSETLINA**[1], S. KWON[3], M. MIRCHANDANI[1], S. BILALOGLU[2], Y. LU[4], R. SUKHOV[5], A. STECCO[1,6], P. RAGHAVAN[5]
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**Abstract:** Brain injury frequently leads to debilitating upper limb dysfunction. Following cerebral injury patients develop muscle weakness and spasticity which is followed by development of muscle stiffness and, if untreated, contractures of the joints. The cause of the muscle stiffness is not fully understood. We proposed the hyaluronan hypothesis, which postulates that stiffness can develop as a result of accumulation of the glycosaminoglycan hyaluronan in the extracellular matrix (ECM) of the muscle, leading to increased ECM viscosity and impaired sliding of muscle fibers during movement. The objective of this study was to determine the extent to which multiple off-label intramuscular injections of the enzyme hyaluronidase, which hydrolyses hyaluronan, could reduce upper limb muscle stiffness, and increase both passive and active joint movement in pediatric patients with brain injury.
In this pilot study ten children (age 7-17) with various etiologies of brain injury, who developed chronic muscle stiffness, received repeated injections of intramuscular human recombinant hyaluronidase into selected upper extremity muscles depending on their clinical presentation, and were followed for 4-24 months following initial intervention. Muscle stiffness, and passive and active range of motion (ROM) at the shoulder, elbow, forearm and wrist were assessed pre-injection, and at a several time points post injection. Muscle stiffness was assessed using the

modified Ashworth scale (MAS) and ROM was video recorded and analyzed using Dartfish video analysis software by two independent researchers. One patient had an allergic skin reaction in the upper arm after the second injection, which required a dose of steroids. All the other patients tolerated the injections without adverse effects.
Muscle stiffness declined by 1 point or more on the MAS after each injection and remained low (0-1 on MAS) at follow up. Overall, 80 passive movements (10 patients, 4 joints, movements in each direction) were analyzed, of which 15 movements had less than 80% of normal range pre-injection. 73.3% (11/15) of these movements improved to within the normal range.
Of the 72 active movements that were analyzed (from 9 patients), 44 were impaired. 61.4% (27/44) of the movements showed significant improvement in extent and control of active range of motion, defined as 20% increase in age-normalized ROM values, or increase by 30 degrees or more, or initiation of movement when there was none pre-injection.
The results of our pilot study suggest that repeated intramuscular hyaluronidase injections can enhance upper limb motor control in patients with muscle stiffness in the chronic stage after brain injury.

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**Poster**

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**Title:** Using clustering algorithms to determine responders to alternate hand training for hand function rehabilitation

**Authors: *P. RAGHAVAN**[1], S. BILALOGLU[2], C. BAYONA[4], A. YOUSEFI[3], A. TANG[5], J. STONE[2], E. BELEN[2], Y. LU[6], A. RANGAN[7]
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**Abstract:** Effective hand function requires a great deal of coordination and control, also an integration of kinesthetic, tactile and visual sensory information with motor output. Over 85% of stroke survivors with hemiparesis have difficulty performing skilled everyday tasks and - despite conventional rehabilitation - have persistent deficits in hand function that severely affect their

quality of life. In previous studies we found that patients post-stroke did not adapt their fingertip forces to object weight with their affected hand. The purpose of this study was to define patient subgroups based on performance on a grasp-and-lift task before and after alternate hand training with objects of varying weights over a single session, and their motor and sensory impairments (in kinesthetic, tactile and visual domains). We recruited 40 patients to perform a grasp and lift task under eight different learning conditions, each involving a different combination of tactile, kinesthetic and visual cues. Each patient practiced the task under each of the treatment conditions with the affected hand only in one session, and then alternating hands in a different session. The measurements include grip and load forces, as well as several clinical tests of tactile, visual, kinesthetic and motor impairment, along with imaging data on brain lesion location and motor tract density. We used a rank-based clustering algorithm to delineate statistically significant patient subgroups which exhibit therapy specific structure. Each of these subgroups will correspond to a 'tricluster' involving not only a specific subset of the patients, but also a specific subset of sensory feedback conditions and grip task outcome measures that respond to alternate hand training. This method pinpoints triclusters within the positively-responding patients that exhibit structure which is not reflected within the non-responding patients. A cluster of patients with primarily motor and tactile deficits on their affected hand showed positive changes in grasp control with alternate hand training under tactile-kinesthetic, tactile-vision-kinesthetic for loading phase (LP), deceleration time (DT) and pre load phase duration (PLD) outcomes. Our results suggest that the patients with different degrees of motor and sensory impairments are likely to require different types of therapeutic regimens and patients with common sensory-motor characteristics may form subgroups that respond preferentially to certain training regimens. Also, the alternate hand training method may allow subjects to use tactile and kinesthetic information from their unaffected hand to improve grasp control in the affected hand.

**Disclosures:** **P. Raghavan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **S. Bilaloglu:** None. **C. Bayona:** None. **A. Yousefi:** None. **A. Tang:** None. **J. Stone:** None. **E. Belen:** None. **Y. Lu:** None. **A. Rangan:** None.

**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 497.18/HH12

**Topic:** E.04. Voluntary Movements

**Support:** UCL BRC MBPhD Funding

**Title:** The influence of prior expectation on movement variability for two different movements

**Authors: *I. C. WEINBERG**[1], S. BESTMANN[2]
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**Abstract:** Preparing multiple movements incurs a cost: movement variability increases when two movements must be planned rather than one (Wijdenes et al., 2016). This can be understood as motor planning using a limited neural resource; when there is more than one motor plan, this limited resource must represent more information, and hence the variability of each representation increases.
We often plan multiple movements which have unequal likelihoods of being executed. An expectation to make one movement over another leads to a reaction time advantage (e.g. Rahnev et al., 2011). A possible explanation is that expectation to move may direct the distribution of a limited resource. We hypothesised that when expectation to make one movement over another is higher, more of the limited resource is allocated to the expected movement and the movement variability is lower.
We tested this in an experiment in which human subjects were required to make a quick, accurate movement to hit one of two visual targets. On each trial, the target that the subject should move to was cued prior to movement. This was preceded by a probability cue, which indicated accurately the relative likelihoods of the target cue being correct (expect left (80:20), expect right (20:80), or expect either (50:50) probability). The two targets were oriented at 45° leftward or rightward in a 2-D plane relative to starting position. Movements were made with the right hand. We were thus comparing a two-joint movement to a single-joint movement (van Beers et al., 2004).
To assess movement variability, we calculated variability in reach angle for movements following the different probability cues. For a leftward, two-joint, movement, early reach angle was indeed less variable when expectation was higher, as hypothesised. The influence of prior expectation ended ~40% through the movement, in line with an effect on motor planning which is strongest early on.
Interestingly, there was no effect of expectation on the early reach angle variability of rightward, single-joint, movements. The different biomechanical properties of one-vs two-joint movements may lead to differing optimal control policies and thus different effects of expectation.
Preliminary results suggest that, for the leftward movement, early position is a stronger determinant of later position than in the rightward movement. This supports the hypothesis that execution noise is less strongly controlled for the rightward movement early on.
We thus propose that a stronger expectation to move influences planning, reducing movement variability, and this effect is dependent on an interaction with the feedback control policy.

**Disclosures: I.C. Weinberg:** None. **S. Bestmann:** None.

**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 497.19/HH13

**Topic:** E.04. Voluntary Movements

**Support:** CREST, JST

**Title:** Perception-action linkage in top athletes during batting

**Authors: *D. NASU**, M. YAMAGUCHI, T. FUKUDA, N. SAIJO, M. KASHINO, T. KIMURA
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**Abstract:** Sports frequently involve severe time constraints. For example, in baseball and softball, a batter is required to judge the characteristics of a pitched ball (i.e., speed and trajectory) and hit it with his/her bat within about 500 ms from the time of pitcher's ball release. Since the pitcher intentionally change the ball speed and trajectory, it is not easy to adjust the timing and position of the bat in relation to an uncertain ball in such a short time. This study evaluated the movement and cognitive features that occur during actual softball batting as regards two types of pitched balls (fastball and change-up), whose different respective ball speeds (approximately 90 and 75 km/h) resulted in a difference of approximately 150 ms in the time between the pitcher's release and bat contact (400 and 550 ms). A superior batter should probably be able to adjust the swing onset to compensate for this time difference. Furthermore, such a superior reaction may result from a superior ongoing ability to perceive ball types traveling with different speeds and trajectories. In this study, we paired the perception task with a real batting task and investigated whether perceptive performance is linked to batting performance. Elite woman's softball players participated in the experiments, and some of them have been members of the national team. In the batting task, the participants were asked to hit randomly pitched fastballs and change-ups. At this time, the batters were not informed of the type of ball would be thrown. The whole body movements of both the batter and pitcher were recorded simultaneously with a motion capture system. In the perception task, the participants stood in the batter's box and faced the same pitcher. They were asked to respond by pressing a button as rapidly as possible whenever the pitcher threw a fastball, but not when the pitcher threw a change-up. As expected, superior batters clearly adjusted the timing of the swing motion to the ball impact according to the pitch type. Specifically, when the pitcher threw a change-up, they paused their swing motion about 300 ms from the time the ball was released and restarted their swing. This was not the case with inferior batters because their swing timing was more variable. The average perception time determined by the participants pressing the button was about 250 ms for superior batters. These times were extremely stable, whereas those for inferior batters were unstable, as was their swing timing. These results indicated that perceptive

repeatability is linked to action stability in a batting situation. It is likely that top athletes have highly reliable perception, which is the underlying basis of high motor performance.

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**Poster**

**497. Cortical Planning and Execution: Reach and Grasp Neurophysiology**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 497.20/HH14

**Topic:** E.04. Voluntary Movements

**Title:** Attentional modulation of visual search alters visuomotor performance without altering limb movements

**Authors: *J. R. NORKITIS**[1], C. PERRY[2], A. HARRISON[2], J. J. FRIDRIKSSON[3], S. L. FRITZ[4], T. M. HERTER[1]
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**Abstract:** Many daily motor tasks, such as driving, use visual search (patterns of eye movements that actively gather visual information) to guide planning and control of limb movements. Visual search is modulated by attentional mechanisms, including “bottom-up” mechanisms that direct eye movements to salient objects and “top-down” mechanisms that direct eye movements to task-relevant objects. The purpose of this study was to examine how attentional modulation of visual search impacts visuomotor task performance. Young adults, older adults, and stroke survivors (left-hemisphere) used a KINARM robot with integrated eye tracking to perform a bimanual visuomotor task, Object Hit and Avoid, in an augmented reality environment. Participants used virtual paddles to hit away Targets objects (n=150) and avoid hitting Distractor objects (n=150) that moved towards them in the horizontal plane. We manipulated the saliency of Targets (task relevant) and Distractors (non-relevant) by altering their brightness relative to the black background (nonsalient, 15% white; salient, 80% white) in five experimental conditions: all objects nonsalient (control), all targets salient (AT), all distractors salient (AD), half targets salient (HT), and half distractors salient (HD). Relative to the control condition, young and older adults exhibited significant increases in task performance (Target Hits) in AT and AD, but similar task performance in HT and HD. Young and older adults also exhibited significant increases in visual search efficiency (Target-Distractor Foveation Bias) and extrafoveal visuomotor performance (Nonfoveated Target Hits) in AT and AD, but not in HT and HD. Measures of limb-motor control were similar across all conditions in the young and older adults. Changes in task performance were strongly correlated with changes in visual search efficiency (young, r=0.65; older, r=0.80) and extrafoveal visuomotor performance (young,

r=0.64; older, r=0.80). Surprisingly, stroke survivors did not exhibit task-dependent modulation on any measure. Our results indicate that: 1) visual search and extrafoveal vision can directly influence visuomotor performance, and 2) post-stroke deficits in attentional mechanisms and/or visual search may contribute to impaired visuomotor performance.

**Disclosures: J.R. Norkitis:** None. **C. Perry:** None. **A. Harrison:** None. **J.J. Fridriksson:** None. **S.L. Fritz:** None. **T.M. Herter:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.01/HH15

**Topic:** E.05. Brain-Machine Interface

**Support:** NIH Grant F32NS093709

NIH Grant R01NS092626

**Title:** Injecting instructions into premotor cortex using intracortical microstimulation

**Authors: *K. A. MAZUREK**, M. H. SCHIEBER
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**Abstract:** When approaching a stop sign, a law-abiding driver responds by moving his or her foot to the brake pedal to stop the car. This is one example of how the nervous system processes information based on learned associations between instructional cues and specific actions. In individuals with neurologic injuries, the ability to process instructions and elicit the associated movements may be damaged or impaired. Instructions typically enter the nervous system through primary sensory modalities, such as vision, hearing, or touch. Recent studies have demonstrated that intracortical microstimulation (ICMS) in the primary somatosensory cortex (S1) can evoke somatotopically localized sensations. ICMS in S1 also has been used to instruct movements, presumably because the subject learns to associate the sensation evoked by ICMS at different S1 sites with particular actions. Can ICMS outside of the primary sensory areas also provide instructions? Here we show that ICMS in the premotor cortex (PM) can instruct specific movements through arbitrary, learned associations. Two monkeys learned to perform particular reach-grasp-manipulate movements instructed by ICMS in PM. The current amplitudes we used for the PM ICMS instructions were too low to evoke muscle activity (confirmed by stimulus-triggered averaging) indicating that the monkeys were not detecting muscle twitches and using them as instructions. Our results show that instructions can be delivered with ICMS in a cortical area not conventionally considered sensory. Additionally, the ICMS did not need to mimic the

natural activity of PM neurons to successfully instruct the movements. The ability to deliver instructions in PM expands the potential territory available for introducing information into the brain artificially. Identifying cortical areas where useful information can be delivered with ICMS eventually may enable development of cortico-cortical neuroprosthetic devices that reestablish communication between areas of a damaged brain.

**Disclosures: K.A. Mazurek:** None. **M.H. Schieber:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** E.05. Brain-Machine Interface

**Support:** NSF EEC-1028725

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WRF Fund for Innovation in Neuroengineering

**Title:** Human perception and psychophysics of direct cortical stimulation of somatosensory cortex

**Authors: *J. A. CRONIN**[1], D. J. CALDWELL[1], G. M. BOYNTON[2], K. E. WEAVER[3], R. P. N. RAO[4], J. G. OJEMANN[5]
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**Abstract: Introduction**: Direct cortical stimulation (DCS) may provide a means of delivering somatosensory feedback in a brain-computer interface (BCI) through electrical stimulation of the primary somatosensory cortex (S1). Previous work has demonstrated that human subjects can perceive and discriminate the intensity of DCS based on varied current amplitude or frequency, and that subjects can use DCS as feedback in a motor task. To effectively integrate somatosensory feedback via DCS into a BCI we must first gain a better understanding of the DCS parameters that can elicit percepts. Here we explore human subjects' DCS perceptual thresholds and their just noticeable differences (JND) in stimulation amplitudes.
**Methods**: Human subjects were implanted with electrocorticography (ECoG) grids (Ad-tech,

Racine, WI) and monitored for long-term seizure activity. We used Tucker-Davis Technologies hardware to deliver bipolar, constant-current stimulation using trains of biphasic square pulses. We varied the current amplitude to quantify subjects' perceptual thresholds and JNDs. We used a staircase method to determine subjects' perceptual threshold and fit the resultant data with a Weibull function using a maximum likelihood method. For the JND assessment we used a two-alternative forced-choice (2AFC) task in which we delivered two 200 ms DCS trains with different current amplitudes separated by 1 s and asked subjects to report whether the "first" or "second" train was more intense.

**Results**: Subjects generally localized the percept to one area on their hand. Subjects' perceptual thresholds ranged from approximately 0.75 mA to 2.0 mA. One subject converged to a 50% perceptual threshold of approximately 0.77 mA (Fig. 1). While this research into the psychophysics of human DCS is ongoing, we anticipate variations in perceptual thresholds between additional subjects. We are continuing to study the effects of current amplitude and other stimulation parameters on subjects' DCS percepts.

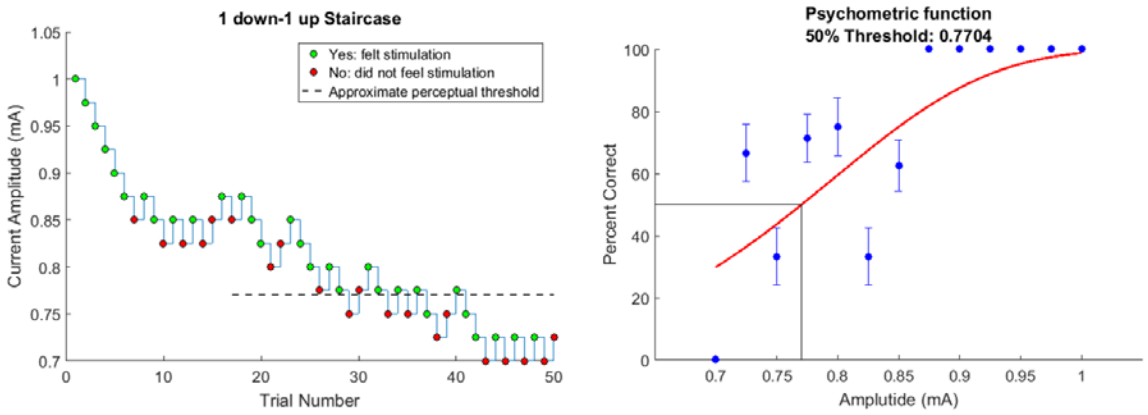


**Figure 1.** Example thresholding staircase and psychometric function for one subject. The 1 down-1 up staircase converges on a 50% threshold which was fit to a Weibull function using a maximum likelihood method. The best fit psychometric function yields a 50% perceptual threshold of approximately 0.77 mA, which is shown on each plot.

**Disclosures: J.A. Cronin:** None. **D.J. Caldwell:** None. **G.M. Boynton:** None. **K.E. Weaver:** None. **R.P.N. Rao:** None. **J.G. Ojemann:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

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**Program#/Poster#:** 498.03/HH17

**Topic:** E.05. Brain-Machine Interface

**Support:** Center for Sensorimotor Neural Engineering, a National Science Foundation Engineering Research Center EEC-028725

Washington Research Foundation UW Institute for Neuroengineering

**Title:** Parameterization of electrical stimulation for modulating intensity of a sensory percept

**Authors: *D. A. BJANES**[1,4], S. KASSEGNE[5,6,4], C. T. MORITZ[2,3,1,4]
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**Abstract:** Current users of brain-computer interface (BCI) technology must rely on visual feedback of cursor or robotic arm movement. The inherently long delays of visual processing likely contribute to relatively slow and unnatural control of BCIs. Despite increasing numbers of electrode sites and ever growing complexity of control algorithms, BCI technology has yet to achieve a rapid, dexterous control signal comparable to an intact human system. We believe the lack of tactile perception and proprioceptive input imposes a fundamental limit on speed and accuracy of BCI controlled prostheses or re-animated limbs. By artificially recreating this comparatively low-latency pathway via Intra-Cortical Microwire Stimulation (ICMS) or micro-ElectroCorticoGraphy (µECoG), BCI stability and control will be improved. Towards this aim, we will explore cortical sensitivity of modulating stimulation parameters to further understand the critical stimulation features which best encode sensory intensity. Given the hi-dimensional parameter space of electrical stimulation, BBCI designers have many options for presenting grated sensation. Parameters such as amplitude, frequency, pulse-width, stimulation train duration, and electrode site could all be modulated to vary the intensity of a percept. Using our novel center-out task for rodents as a behavioral metric of perceived intensity, we can compare the perceptual resolution of modulating these parameters, both individually and combinatorically. Rodents perform discrimination tasks to measure just-noticeable-differences (JNDs) and perceptual thresholds. By understanding the mapping between parameter modulation and sensory perception of intensity, we can identify the critical parameters which sensory cortex cues off when presented with electrical stimulation, either through penetrating micro-wires or on the surface of the brain.
Our overarching goal is to formulate a general pattern for providing a high resolution sensory signal which can be mapped to any sensory modality. Through electrical stimulation, either on the surface (µECoG) or through penetrating wires (ICMS), we will repair/create this low-latency sensory feedback in our BCI control loop. This will enable patients with a wide range of impairments, from spinal cord injury, stroke, to any user of BBCI technology. By improving their control of a prosthetic (or re-animated) limb, we can integrate this into existing BBCI implementations and increase our knowledge of augmented sensory prosthetics.

**Disclosures: D.A. Bjanes:** None. **S. Kassegne:** None. **C.T. Moritz:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

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Washington Research Foundation Funds for Innovation in Neuroengineering

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NSF DGE-1256082

**Title:** Spectrotemporal analysis of direct cortical stimulation compared to haptic stimulation in a response timing task in humans

**Authors: *D. J. CALDWELL**[1,7], J. A. CRONIN[1,7], J. WU[1,7], J. N. KUTZ[2], B. W. BRUNTON[3,7], K. E. WEAVER[4,7], R. P. RAO[5,7], J. G. OJEMANN[6,7]
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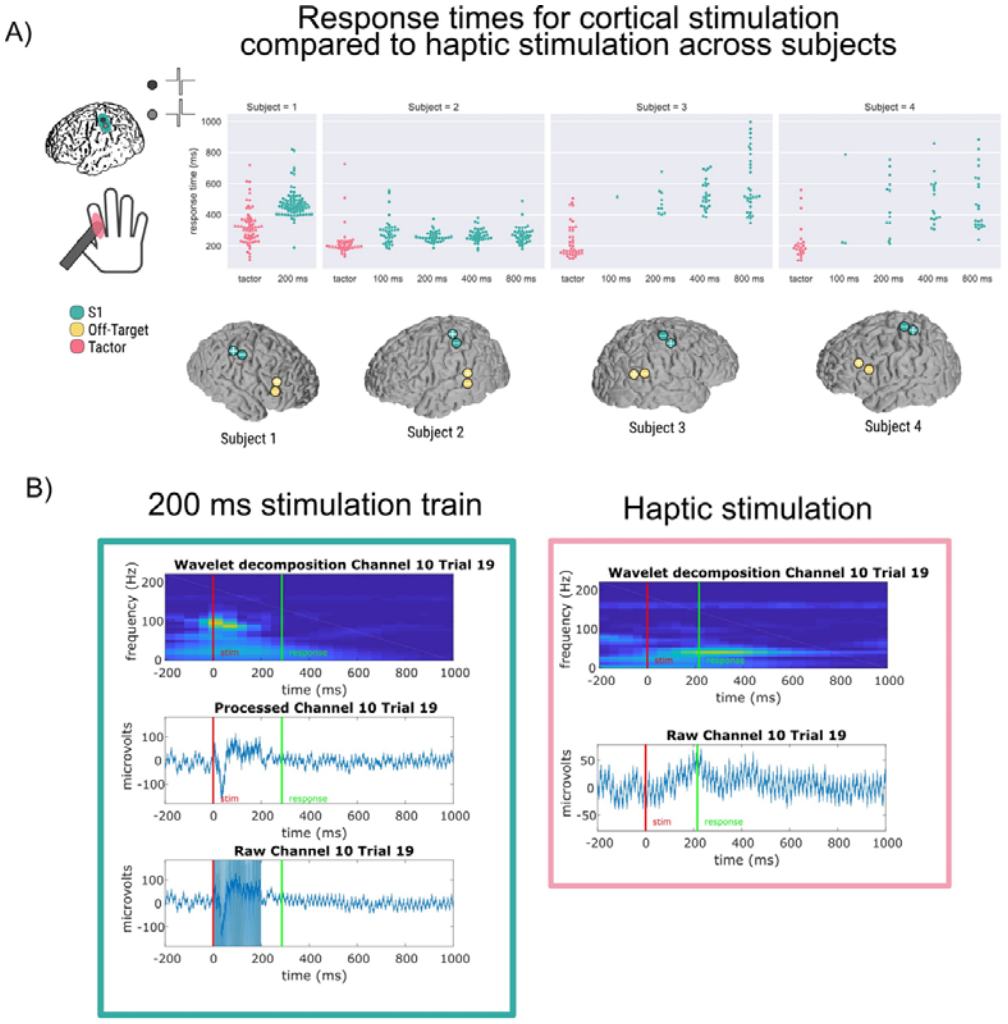
**Abstract:** Objective: Direct cortical stimulation (DCS) may help close the loop in human brain computer interfaces. Previous efforts have shown that humans can respond to and utilize DCS to somatosensory (S1) cortex to perform a task while non-human primate work using intracortical stimulation revealed a delayed reaction time for cortical stimulation compared with haptic stimulation. However, the comparison of human S1 DCS to haptic stimulation has not been explored. In this study we examine and compare psychometric response timings and spectro-temporal analyses of human electrocorticographic (ECoG) signals for DCS of hand somatosensory cortex and haptic stimulation. Methods: Humans (n=4) were implanted with ECoG grids for epilepsy monitoring. We provided haptic stimulation through digital touch probes (tactors) to the same cutaneous region where sensation was reported through DCS (200 Hz, biphasic, bipolar stimulation) to S1 hand cortex. Train lengths of 200 ms DCS were applied to one subject, with trains of 100, 200, 400 and 800 ms in the subsequent 3 subjects in 2 separate blocked trials. In the 3 later subjects, off-target stimulation of a region outside of S1 was used as a control. An optimized ICA algorithm was used for post-hoc neural signal extraction during

stimulation trials. Spectrotemporal analyses were performed with wavelets. Results: Haptic stimulation elicited significantly faster reaction times (RT) than cortical stimulation across all subjects (Fig. A). DCS trains of different lengths did not result in significantly different RTs. No significant block wise differences were seen. Individual trial spectrotemporal analyses demonstrate post-stim signal differences between haptic and stimulation conditions (Fig. B). Conclusions: These results show that the perception of direct cortical stimulation in humans is significantly slower than haptic stimulation. Different spectral responses to haptic relative to cortical stimulation are suggestive of non-native patterns of neural activity elicited by cortical stimulation, potentially explaining slower response times.




A) Individual subjects' response times and cortical reconstructions showing S1 and off-target stimulation sits. Only one off-target stimulation was responded to in Subject 2, with no other responses in the other subjects. Individual points represent individual response times per trial.

B) Example trial with optimized ICA processing for neural recording extraction during the stimulation period, compared to a haptic stimulation trial in an electrode adjacent to the stimulation electrodes in Subject 2.

**Disclosures:** **D.J. Caldwell:** None. **J.A. Cronin:** None. **J. Wu:** None. **J.N. Kutz:** None. **B.W. Brunton:** None. **K.E. Weaver:** None. **R.P. Rao:** None. **J.G. Ojemann:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.05/HH19

**Topic:** E.05. Brain-Machine Interface

**Support:** 5R01NS072343-02

N66001-11-C-4171

**Title:** Hind-limb motor responses to microstimulation of the dorsal root ganglia in behaving cats

**Authors: *M. A. URBIN**, A. C. NANIVADEKAR, K. K. KING, W. D. CUSACK, M. F. LIU, R. A. GAUNT, L. E. FISHER, D. J. WEBER
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**Abstract:** A lack of cutaneous and proprioceptive feedback impedes the ability to control lower-limb prosthetics, thus, impairing gait and increasing the risk of falls. Recent work has demonstrated that microstimulation of the dorsal root ganglia (DRG) selectively recruits major hind-limb nerve branches early (Gaunt et al., 2009; Ayers et al., 2016) and months after implantation (Fisher et al., 2014). Patterned microstimulation of the DRG may therefore provide a means to generate sensory percepts for an advanced lower-limb neuroprosthetic. Since patterns of lower-limb muscle activation during gait are largely mediated by somatosensory inputs (Duysens & Stein, 1978), the ability to drive motor responses may further increase the functionality of such a device. Here, we report on motor responses evoked by DRG microstimulation in awake, behaving animals. Penetrating, 32-channel microelectrode arrays were implanted chronically in the L6 and L7 DRG of four male cats. EMG electrodes were implanted in the ipsilateral flexor and extensor muscles of the knee and ankle, and the sciatic nerve was instrumented with a five-contact nerve cuff. A binary search procedure was performed on stimulating channels during anesthetized experiments each week to determine sciatic nerve recruitment threshold. A stimulating electrode with low threshold for recruiting Group I afferents was selected for delivering 10-ms, 100-Hz pulse trains at 1.5x (ie, stimulation-low) and 2.0x (ie, stimulation-high) threshold while the cat was standing on a platform in subsequent experiments each week. Motor-evoked responses were defined as a sustained change in the EMG signal ($\geq$20 ms) that was $\geq$2 standard deviations above/below the mean of the pre-stimulation window (200 ms). Over the course of testing (15.8±1.3 weeks), motor responses were observed in stimulation-low (25.1±10.5%) and stimulation-high (26.7±14.8%) conditions. Across both conditions, a comparable response rate was found in knee (33.5±16.1%) and ankle (38.3±20.1%) muscles with flexor (37±18%) or extensor (31.9±19.2%) joint actions. Motor responses exhibited were mostly facilitatory (63.6±15.2%) and fewer were inhibitory (19.5±15.6%). Some responses consisted of

both facilitation and inhibition (16.8±16.6%). The various patterns of motor responses likely reflect activation of multiple spinal reflex circuits, including those involved with monosynaptic Ia excitation, disynaptic reciprocal inhibition, and recurrent inhibition. Further work is needed to understand how DRG microstimulation can selectively activate each spinal circuit to allow for maintenance of balance and effective sequencing of gait transitions.

**Disclosures:** **M.A. Urbin:** None. **A.C. Nanivadekar:** None. **K.K. King:** None. **W.D. Cusack:** None. **M.F. Liu:** None. **R.A. Gaunt:** None. **L.E. Fisher:** None. **D.J. Weber:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.06/HH20

**Topic:** E.05. Brain-Machine Interface

**Support:** DARPA Contract N66001-10-C-4056

DARPA Contract N66001-16-C-4051

**Title:** Artifact-free recording during human intracortical microstimulation

**Authors: *J. M. WEISS**[1,2], R. FRANKLIN[3], S. N. FLESHER[2,4], J. L. COLLINGER[1,2,4,5], R. A. GAUNT[1,2,4]
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**Abstract:** We have previously demonstrated brain-computer interface (BCI) control of a robotic arm using signals recorded from motor cortex (M1) and that intracortical microstimulation (ICMS) of human primary somatosensory cortex (S1) can evoke tactile percepts. We wish to combine these results in a closed-loop BCI system, which must be capable of continuously recording and stimulating adjacent regions of cortex. This problem is non-trivial due to the presence of large amplitude electrical stimulus artifacts, which mask smaller-amplitude extracellular potentials generated by active neurons. Additionally, filtering of the recorded signals, an essential step for spike detection, can compound the problem by distorting artifacts in time such that the signal is corrupted for a duration longer than the stimulus pulse width. We developed a simple artifact elimination (AE) scheme to record in M1 during ICMS of S1 without complex real-time processing.
A man with a C5/C6 spinal cord injury was implanted with two recording microelectrode arrays in M1 and two stimulation microelectrode arrays in S1. During each 700 µs biphasic stimulus

pulse, a sample-and-hold digital filter was applied to the raw recorded signal to eliminate stimulus artifacts prior to additional filtering. A 750 Hz first-order high-pass Butterworth filter was then applied to the signal prior to thresholding for spike detection. These parameters were chosen to meet the specifications of a fast return to baseline after perturbations, elimination of filter ringing in the step response, and an overall increase in signal-to-noise.
This AE scheme allowed for reliable spike detection as soon as 800 μs after the offset of each stimulus pulse, corresponding to a 15% loss of neural data when stimulating at 100 Hz. We demonstrated the effectiveness of the AE scheme in a closed-loop BCI task. A 5 DOF velocity decoder was trained to control a robotic arm. The subject was instructed to use the robotic arm to transfer an object across a 20 cm region as many times as possible during a two-minute period. During ICMS trials, 8 electrodes were simultaneously stimulated between 18-46 μA at 100 Hz when the fingers generated torque against the object. A one-way ANOVA found significant differences in performance between baseline (no ICMS), ICMS, and ICMS+AE conditions ($p < .01$). Post-hoc tests revealed a significant decrease in performance with ICMS without AE compared to baseline ($p < .01$), but no significant difference between baseline and ICMS+AE conditions ($p = .621$).
The proposed system is relatively simple to implement and requires minimal parameter tuning to produce reliable recordings during ICMS for closed-loop BCI control.

**Disclosures:** **J.M. Weiss:** None. **R. Franklin:** A. Employment/Salary (full or part-time):; Blackrock Microsystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock Microsystems. **S.N. Flesher:** None. **J.L. Collinger:** None. **R.A. Gaunt:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.07/HH21

**Topic:** E.05. Brain-Machine Interface

**Support:** NIH Grant NS095251

**Title:** Sub-millisecond electrical recordings of neural responses to stimulation with intracortical microelectrode arrays in somatosensory cortex

**Authors: *J. SOMBECK**[1], T. TOMLINSON[2], A. V. PETERCHEV[4,5,6,7], W. M. GRILL[5], L. E. MILLER[1,2,3,8]
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**Abstract:** Intracortical microstimulation (ICMS) is a powerful tool both to probe neural circuits and to produce artificial sensations in a brain machine interface (BMI) for a variety of modalities, including vision, audition, touch and proprioception. In addition to conscious perception, the role of somatosensation in the control of movement in bidirectional BMIs is of potentially great importance. When used to provide somatosensory feedback, ICMS through an array of electrodes implanted in the somatosensory cortex (S1) could be used to evoke neural activity that closely imitates that of natural limb movements. This biomimetic approach is appealing as it may elicit intuitive sensations that require less learning to master. To maximize the effect of biomimetic approaches, it is important to understand the response of cortical neurons to ICMS. This is a challenge, as the electrical artifacts associated with ICMS typically prevent obtaining electrical recordings for several milliseconds after the stimulation pulse. We evaluated the effect of various front-end electronics, post-processing techniques, and stimulation profiles on the electrical artifact generated by ICMS when using chronically implanted 96-channel electrode arrays in S1 of rhesus monkeys. We varied the timing and amplitude of the pulse charge balance, resulting in stimulation profiles that decreased the duration of the artifacts on both the stimulated and non-stimulated electrodes. Additionally, by using a lower gain pre-amplifier, we reduced the loss of signal due to saturation. This is most critical immediately after stimulation pulses end, as avoiding saturation improves linearity and reduces the latency at which it is possible to resume recording neuronal activity. To make the post-stimulus data more accessible, we used acausal, time-reversed filtering to attenuate slowly decaying artifacts without contaminating the post-stimulus period with the filter transient response to the stimulus. We implemented this process in quasi-real time with about a 70 ms delay. Using these approaches, we developed methods that allowed stimulation and recording at sub-millisecond latencies even within an array of electrodes. We were able to record on non-stimulated electrodes about 0.4 ms after the end of the stimulation pulse and on the stimulated electrode about 1 ms after the end of the pulse. Using these tools, we have begun to explore the spatial pattern of neural responses to stimulation. This work enables the development and validation of models to design stimulation patterns to evoke biomimetic cortical activity that closely imitates that of natural limb movements.

**Disclosures: J. Sombeck:** None. **T. Tomlinson:** None. **A.V. Peterchev:** None. **W.M. Grill:** None. **L.E. Miller:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.08/HH22

**Topic:** E.05. Brain-Machine Interface

**Support:** DARPA W911NF-15-2-0054

**Title:** A neuromodulation integrated circuit for high-channel count, bidirectional, and minimally invasive neural interfaces

**Authors: *S. JUNG**, E. ALON, J. RABAEY
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**Abstract:** We present a neuromodulation integrated circuit (IC) as a key building block in realizing a neural interface. The IC has 64 low-power small-area digitally programmable recording channels (<3uW/channel, 150umx150um/channel, variable BW, variable gain, AC-coupled), two digitally programmable stimulators (current digital-to-analog converter, variable phase, variable amplitude, variable pulse width, and variable pulse rate, multiplexed to eight different sites), and digital blocks for wired communication between the IC and a field-programmable gate array (FPGA). On-chip powertrains provide regulated supply voltages to recording channels and digital communication blocks, and also high-voltage supplies to the stimulators. This tight integration makes the IC as one of the most dense (4.78mm$^2$) and low-power (<1mW) hardware.
By attaching the low-power dense neuromodulator IC and fine flexible microelectrodes on a small flexible printed circuit board (PCB), we get a prototype hardware that can be implanted on a brain with being minimally invasive. We target to separately insert >1000 flexible microelectrodes, increasing observability and controllability of electrical neural signals. Multiple ICs and PCBs are deployed to support 1000-channel recording. All the recorded signals are first serialized in the ICs, and the FPGA time-multiplex data streams of each IC to relay the data to a PC. For stimulation, commands are asserted from the PC, relayed by the FPGA, and get activated in the IC. USB3.0 link is used between the FPGA and the PC for this purpose. This integrated system realizes the microelectronics part of a 1,000-channel bidirectional neural interface we envision.

**Disclosures: S. Jung:** None. **E. Alon:** None. **J. Rabaey:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.09/HH23

**Topic:** E.05. Brain-Machine Interface

**Support:** JST KAKENHI 15K12576

JST KAKENHI 17K17684

**Title:** Study on the deep brain stimulation to induce voluntary locomotion of a rat

**Authors: *N. SUDO**, O. FUKAYAMA, K. MABUCHI, Y. ABE
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**Abstract:** The brain-machine interface (BMI) with transcranial electrodes is a powerful method to extract motor commands in the brain to control the body. Supervised estimators have been generally used to correlate neural activities with the voluntary intentions to move the limbs. However, it is not easy to regulate the intentions of experimental rodents, commonly used for invasive BMI experiments, to move the body parts. This work proposes a method to motivate a rat to make a voluntary locomotion by applying electrical stimuli in the deep brain region. For surgical preparation, a pair of wire electrodes implanted in the deep brain of a rat, 2.5 mm posterior, 2.0 mm lateral, and 8.0 mm ventral from the brain surface of the bregma point in the stereotaxic coordinate system. Then, the rat was connected to an electrical stimulator (Multichannel Systems STG-4008) while it behaved freely on a plain field of 150 cm wide and 150 cm depth. An optical recorder system tracked two LEDs attached to the top of the head to detect forward body movements. The locomotion velocity over the 15 cm/s threshold drove the stimulator to flow biphasic spike trains of electric currents in the brain. The rat initially had a sham period of 15 minutes followed by an active period of 15 minutes where the stimuli were applied. The set were conducted twice to 3 times per a day. As a result, close to half out of the tested rats increased frequency of the voluntary locomotion in the active periods. They tended to walk around the field to earn more stimuli in the brain, which ceased as the stimuli were stopped in the next sham period. The tendency repeated in the sets on the following days. Meanwhile, continuous stimuli asynchronous to the body movement were ineffective. The others which failed to gain the tendency to walk included a subject which learned to shake its head instead of walking to earn false detection of the LED movements, a subject which showed involuntary movement of the neck to interfere with walking. The remainders showed no responses to the stimuli regardless of the active and sham periods. These results suggest that stimulation in the deep brain changed behavioral tendency of the rats. Its reason was considered that they learned walking as a behavior to get reward because the tip of the electrodes located in the lateral hypothalamus, known as a reward area. The failed subjects were supposed to have electrodes placed in inappropriate positions. Our method could have temporarily induced the locomotion without altering the original circuits of the rats, and may be utilized to train BMI estimators.

**Disclosures:** **N. Sudo:** None. **O. Fukayama:** None. **K. Mabuchi:** None. **Y. Abe:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.10/HH24

**Topic:** E.05. Brain-Machine Interface

**Support:** DARPA N66001.16.C.4051

Revolutionizing Prosthetics Program N66001.10.C.4056

**Title:** The complex relationship between frequency and perceived magnitude of intracortical microstimulation in human somatosensory cortex

**Authors: *C. L. HUGHES**[1], S. N. FLESHER[1], J. M. WEISS[1], M. BONINGER[2,3], J. L. COLLINGER[1,2,3], R. GAUNT[1,2]
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**Abstract:** It is difficult to grasp and manipulate objects without tactile feedback, and yet prosthesis users must work with this limitation. To work towards a solution, we implanted microelectrode arrays in primary motor (M1) and primary somatosensory (S1) cortices in a person with a cervical spinal cord injury to enable closed-loop prosthesis control. Using neural activity decoded from M1, our participant can control a dexterous prosthetic limb while sensory feedback is delivered through intracortical microstimulation (ICMS) in S1. Microstimulation on more than 60 of the 64 implanted electrodes reliably evokes sensations in the hand, but the perceived intensity of the stimuli evoked can vary significantly from electrode to electrode. We have previously shown that stimulation amplitude has a linear relationship to perceived intensity, but the stimulation frequency was always 100 Hz. In non-human primates increasing stimulation frequency decreases detection thresholds, but has little effect on discriminability. [1] It has also been suggested that increasing stimulus frequency could increase perceived intensity. Here we explored the effects of stimulus frequency on perceived magnitude in a human participant. To test this, we used a free magnitude estimation task where varying stimulus amplitudes (20, 50, and 80 uA) and frequencies (20, 100, and 300 Hz) were paired and presented in randomized order. For each stimulus pair, the participant reported the perceived intensity on a self-selected scale. We found that that perceived intensity increased with stimulation amplitude on all electrodes at all frequencies, as expected. However, stimulus frequency changed the perceived intensity in idiosyncratic ways that were electrode dependent: when comparing between 20 and 100 Hz, on 3 of 8 stimulated channels, 20 Hz was associated with increased perceived intensity, while on 5 of 8 stimulated channels, 100 Hz was associated with increased perceived intensity and these relationships generally held across all stimulus amplitudes. Understanding the relationships between stimulus frequency, perceived intensity, and other perceptual characteristics could help us improve the perceptual quality of ICMS and develop prostheses that provide a rich sensory repertoire. Ultimately, these techniques could also help us understand how inputs are processed more generally in the somatosensory cortex. [1] S. Kim, T. Callier, G. A. Tabot, R. A. Gaunt, F. V. Tenore, and S. J. Bensmaia, “Behavioral assessment of sensitivity to intracortical microstimulation of primate somatosensory cortex.,” Proc Natl Acad Sci USA, p. 201509265, Oct. 2015.

**Disclosures: C.L. Hughes:** None. **S.N. Flesher:** None. **J.M. Weiss:** None. **M. Boninger:** None. **J.L. Collinger:** None. **R. Gaunt:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.11/HH25

**Topic:** E.05. Brain-Machine Interface

**Support:** DARPA Contract Number N66001-10-C-4056

DARPA Contract Number N66001-16-C-4051

**Title:** Effects of intracortical microstimulation feedback on functional task performance during human brain-computer interface control

**Authors: *S. N. FLESHER**[1], J. E. DOWNEY[1], J. M. WEISS[2], A. J. HERRERA[3], C. L. HUGHES[3], M. L. BONINGER[2], J. L. COLLINGER[4], R. A. GAUNT[2]
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**Abstract:** Brain-computer interfaces (BCI) have enabled users to achieve high degree-of-freedom control of a prosthesis even though limb state feedback has been limited to information available through vision. In tasks such as object manipulation however, providing tactile sensory feedback is an important step to improving control as vision provides less salient cues. Intracortical microstimulation (ICMS) of area 1 of primary somatosensory cortex (S1) can convey spatially selective tactile percepts that are graded over a range of perceived intensities and may therefore be sufficient for providing information about object contact force. Here we demonstrate that ICMS in S1 can be used during continuous control of a BCI to provide task-relevant feedback about both the location and intensity of object contact.
In this study, a twenty-eight year old participant with a chronic C5 motor and C6 sensory spinal cord injury was implanted with two intracortical microelectrode arrays in primary motor cortex (M1) and two arrays in S1. The M1 arrays were placed in the upper limb representation and used to continuously control various BCI end effectors. The S1 electrode arrays were targeted to the hand region of area 1 in the left hemisphere based on presurgical imaging. The goal was to elicit cutaneous percepts that project to the fingers of the right hand.
In a first task, we found that simple cursor control tasks where the subject attempted to locate an unseen target that provided ICMS feedback could be completed under the guidance of stimulation alone. Further, functional tasks, such as object transfers, were performed with and without ICMS feedback. In these tasks, robot finger torques were read every 20 ms and linearly mapped to ICMS pulse amplitudes to relay information about object contact. These tasks were performed at least as well with ICMS feedback as they were without it. We have found that simple tasks where vision is obscured and task feedback is only available through ICMS clearly

show the value of providing ICMS feedback. However, in more complex tasks where vision is available, ICMS feedback has not always improved performance. While our participant prefers having ICMS turned on, functional gains are currently difficult to quantify. Significant future work remains in identifying non-trivial tasks that are within the motor control capacity of current BCIs and the end effectors they control, yet can still benefit from cutaneous sensory feedback.

**Disclosures: S.N. Flesher:** None. **J.E. Downey:** None. **J.M. Weiss:** None. **A.J. Herrera:** None. **C.L. Hughes:** None. **M.L. Boninger:** None. **J.L. Collinger:** None. **R.A. Gaunt:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.12/HH26

**Topic:** E.05. Brain-Machine Interface

**Support:** NSF Grant 1551239

**Title:** StimDust: An ultrasonically powered neural stimulator with temporally precise waveform control

**Authors: *B. C. JOHNSON**, *B. C. JOHNSON, K. SHEN, D. K. PIECH, M. GHANBARI, K.-Y. LI, R. NEELY, J. M. CARMENA, M. M. MAHARBIZ, R. MULLER
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**Abstract:** A major technological barrier to ubiquitous and chronic brain-machine interfaces or peripheral nerve electroceuticals embedded deeply in soft tissue is a bi-directional, wireless system on a sub-mm scale. To address this challenge, we circumvented the size-scaling issues and energy absorption losses associated with conventional EM systems and developed an ultrasonically powered neural stimulator, Stimulating Neural Dust (StimDust). Each StimDust mote consists of a 750μm x 750μm piezocrystal for power harvesting and communication packaged with a 1mm x 1mm power-efficient control ASIC (application specific integrated circuit) on a flexible printed circuit board.
Previous implementations of ultrasonically-powered stimulators provided uncontrolled stimulation sensitive to received power and electrode impedance. StimDust, however, rectifies and stores power harvested from the piezocrystal and utilizes a current-mode stimulator to deliver a controlled charge independent of electrode size and impedance. Furthermore, the stimulation waveform is dynamically reconfigurable via the structure of the input ultrasound, where lengths of ultrasonic packets encode commands for amplitude, frequency, pulse width, and interphase gap. This enables temporally precise (sub-microsecond) control of pulse width, interphase gap, and pulse interval. Another advantage of using ultrasound to encode control

signals is the flexibility and inherently high dynamic range afforded to the stimulation frequency (e.g. 1mHz to 10kHz) without relying on internal clock dividers which consume power and are sensitive to the resonant frequency of the piezocrystal. The system can deliver up to 350μA of stimulation current at a wide range of pulse widths and frequencies, resulting in a >80% conversion efficiency from received power to delivered stimulation power.

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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.13/HH27

**Topic:** E.05. Brain-Machine Interface

**Support:** DARPA N66001-10-C-4056

**Title:** Navigating a virtual environment using intracortical microstimulation of human somatosensory cortex

**Authors: E. A. POHLMEYER**[1], M. S. FIFER[1], S. J. BENSMAIA[2], M. RICH[1], J. PINO[1], S. N. FLESHER[3], J. M. WEISS[4], J. L. COLLINGER[5], R. A. GAUNT[4], J. BEATY[1], M. MCLOUGHLIN[1], *F. TENORE[1]
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**Abstract:** Brain-Computer Interface (BCI) systems have been developed that allow users to control devices such as computer cursors, robotic manipulators, and advanced upper limb prosthetics such as the Modular Prosthetic Limb (MPL). Typically, the only information available to the BCI user regarding the state of the device is from the visual system. However, recent studies have shown that intracortical microstimulation (ICMS) can be used to provide feedback about the state of the BCI. Many questions remain, however, about the potential of ICMS to convey information about complex actuators that can adopt many states (e.g. upper limbs).
We explored whether a BCI user with tetraplegia could position the hand of a virtual MPL (vMPL) over an invisible, randomly positioned target in a 2D plane when guided solely by ICMS. The vMPL hand position was controlled via neural signals recorded from multi-electrode arrays implanted in primary motor cortex, while ICMS was delivered through multi-electrode arrays implanted in primary somatosensory cortex. Two approaches were used to provide

information to the subject regarding the position of the hand relative to the target: proximity and direction. In the proximity mapping, ICMS amplitude on a single electrode increased in six discrete levels as the vMPL approached the target. In the direction mapping trials, target position relative to the vMPL's current location was conveyed through three ICMS channels. Each channel was assigned a particular angular direction ($90^O$, $210^O$, $330^O$). The amplitude for each channel was scaled (in six discrete levels) by relating the angle of an ideal target movement (given current vMPL position) to the channels' associated directions. Stimulation frequency was 100 Hz, and charge-balanced pulses with a cathodal phase of 200 µs were used. The BCI user was able to learn to use the ICMS to guide movements using both the proximity and direction mappings. In both cases, the subject achieved accuracies which significantly outperformed chance (*p* < 0.05). While the BCI user achieved higher target accuracies using the proximity-based encoding scheme, the distribution of vMPL movements during direction-encoded trials still showed a clear bias toward the angles communicated via ICMS. Our results highlight that encoding strategy is critical in designing feedback for BCIs: some strategies are more intuitive and thus easier to learn.

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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.14/HH28

**Topic:** E.05. Brain-Machine Interface

**Support:** Charles Stark Draper Laboratory

**Title:** Wireless stimulation of pelvic floor motor efferents neuromodulate micturition in female rabbits

**Authors: *A. G. HERNANDEZ REYNOSO**[1], D. L. CORONA QUINTANILLA[2], F. CASTELÁN[3], M. MARTINEZ-GOMEZ[4], D. K. FREEMAN[5], S. F. COGAN[6], M. I. ROMERO-ORTEGA[7]
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**Abstract:** More than 40% of women suffer from lower urinary tract (LUT) disorders including deficient bladder emptying and urinary incontinence. Electrical stimulation of the S3-S4 root or the pudendal plexus that innervate several pelvic and perineal targets is considered currently a viable alternative treatment of several LUT dysfunctions. However, this therapy seems to increase urinary retention in some patients, and urinary voiding in others. These contradictory effects seem to be, at least in part, due to the indiscriminatory activation of both efferent and afferent fibers in the sacral or pudendal plexi in the pelvic floor. We sought to investigate whether stimulation of the specific motor efferent innervating the ischiocavernosus, (Ism) and bulbospongiosus (Bsm) muscles in the pelvic floor would modulate the bladder emptying response. Since our previous studies demonstrated that, these muscles deploy asynchronous activity during urine storage and bladder emptying. Nulliparous adult young female rabbits were implanted acutely with a novel wireless miniature cuff electrode (WMCE) that uses RF at a 10.7 MHz frequency to power a 1 mm transistor-less device attached to a custom nerve cuff. A diode in the WMCE was used to produce a 400 us cathodic pulse and deliver a 400 mV potential to the target nerves. The animals were stimulated for 30 seconds at 2 Hz and repeated 3 times with a 10-minute inter-stimulation delay. Cystometrograms were recorded before and during the WMCE stimulation and the threshold volume of the bladder, voided and residual volume, and the voiding efficiency were quantified. The results showed that wireless stimulation of the Bsm and Ism nerves the increase the maximum pressure of the bladder. These results demonstrate the efficacy of wireless neuromodulation of perineal muscle nerves for affecting bladder function and suggest that this approach might offer a more selective treatment for urinary incontinence.

**Disclosures: A.G. Hernandez Reynoso:** None. **D.L. Corona Quintanilla:** None. **F. Castelán:** None. **M. Martinez-Gomez:** None. **D.K. Freeman:** None. **S.F. Cogan:** None. **M.I. Romero-Ortega:** None.

**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.15/HH29

**Topic:** E.05. Brain-Machine Interface

**Support:** DARPA N66001-17-2-4010

**Title:** Evaluation of a neural interface for electrical stimulation of the mouse infraorbital nerve

**Authors: A. J. SUMINSKI**[1], J. NOVELLO[3], S. K. BRODNICK[4], J. NESS[2], W. ZENG[5], J. PISANIELLO[3], A. M. DINGLE[5], S. O. POORE[5], W. B. LAKE[1], *J. C. WILLIAMS[3]
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**Abstract:** The trigeminal nerve (CN V) is divided into three branches, opthalmic (V1), maxillary (V2) and mandibular (V3), and carries most of the tactile, proprioceptive and nociceptive information from sensors in the face to the central nervous system via nuclei in the brainstem and thalamus. In recent years, the V1 branch of the trigeminal has become a popular target for neuromodulation therapies to treat of a variety of neurologic and psychiatric disorders (i.e. epilepsy, depression, attention deficit hyperactivity disorder and traumatic brain injury) due to its integration with the sympathetic and parasympathetic nervous system. Despite promising preclinical and clinical data, the mechanism of action trigeminal nerve stimulation (TNS) remains in question. In this work, we describe the development and evaluation of a neural interface targeting the mouse trigeminal nerve with the goal of enabling future mechanistic research on TNS. We performed separate experiments designed to: 1) identify the best stimulation target for TNS in the mouse and 2) evaluate the ability of a cuff electrode to stimulate the nerve. Using fresh cadavers, we investigated the course and measured the size of each branch of the trigeminal nerve, and found that V2 (infraorbital branch) was the best candidate for a neural interface to its accessibility and size (0.7mm diameter). In contrast, V1 is easily accessible (supraorbital branch) but rather small (0.2mm diameter), while the course of the V3 branch (behind the lower jaw) makes access problematic. To evaluate our ability to engage the infraorbital nerve, mice were anesthetized with isoflurane (1-2.5%) and implanted with a custom bipolar cuff electrode (1.5mm spacing, 0.05mm wire diameter) on the infraorbital nerve distal to the infraorbital foramen. Electrical stimulation of the infraorbital nerve was performed using single, monophasic or biphasic (cathode leading) pulses (50-800uA, 100-300us per phase) initiated at pseudorandom intervals (varying between 3-4 seconds). Following surgery, anesthesia was switched from isoflurane to a ketamine (25-100mg/kg) - dexmedetomidine(0.05-0.1mg) cocktail. We measured changes in cortical activity in the barrel cortex (somatosensory evoked potentials [SSEPs]) elicited by stimulation using a uECoG array (16 channel, 200um site diameter, 500um inter-site spacing). The magnitude of SSEPs increased monotonically until saturation with increases in stimulation current and activation thresholds decreased with increases in phase duration. These preliminary results suggest that an infraorbital nerve interface is a suitable candidate for examining the neural mechanisms of TNS in the mouse.

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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.16/HH30

**Topic:** B.10. Network Interactions

**Support:** NIBIB 1R01EB018297 (MRZ)

NIMH DP2 OD017661 (SJA)

NSF GRFP DGE 1256260 (JPR)

Rackham Merit Fellowship (JPR)

**Title:** Sub-threshold resonance organizes activity and optimizes learning in neural networks

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**Abstract:** Oscillations in field potentials provide insight to the underlying information processing within regions of the brain. A huge catalog of experimental evidence has shown that coordination of oscillations across and within brain areas is critical for learning and performance in memory tasks. While a large amount of work has focused on the generation of neural oscillations, the effect that these oscillations have on the spiking activity of neural populations and the extent to which these rhythms have a direct role in the learning process has not been evaluated. In the present work, we propose that a neuronal property, sub-threshold resonance, interacts with oscillating input to ensure that networks of neurons properly map the information represented in external inputs the weights of recurrent synaptic connections. We demonstrate using a biophysical neuronal model that when individual cells display an input-current dependent shift in their resonance response, populations will arrange their phases of action potential firing to represent the differences in the strengths of their respective inputs. As networks learn (i.e. change synaptic strengths to compensate for the differences in external input) the firing phase difference is reduced to a minimum. Consequently, learning saturates when the network has successfully mapped the input distribution to the synapses. Additionally, we show that by bringing consecutive subsets of neurons into and out of resonance with an oscillating input allows networks to accurately store and reproduce sequences of activation in both the forward and reverse direction, as seen in numerous experimental studies. As validation for our proposed mechanism we show *in vivo* that periodic stimulation of hippocampal cells coordinates network

activity and functional connectivity in a frequency-dependent manner that is qualitatively reproduces the effect seen modeled networks. We argue that sub-threshold resonance provides a emergent network level mechanism to accurately encode and retrieve information without over-strengthening connections between neurons.

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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.17/HH31

**Topic:** E.05. Brain-Machine Interface

**Support:** This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) MTO under the auspices of Dr. Jack Judy through the Space and Naval Warfare Systems Center, Pacific Grant/Contract No. N66001-11-C-4171.

**Title:** Microelectrode arrays chronically implanted into feline peripheral nerve elicit a characteristic response

**Authors:** ***C. L. KOLARCIK**[1], C. A. CASTRO[2], A. LESNIAK[1], A. J. DEMETRIS[1], D. J. WEBER[1], L. E. FISHER[1], X. T. CUI[1], R. A. GAUNT[1]
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**Abstract:** Neural interfacing technologies have the potential to significantly improve the quality of life of patients that are severely disabled or suffering from a variety of neurodegenerative conditions. To recapitulate proper physiological function, motor commands and sensory feedback must be considered. The spinal nerve is a unique location at which these complementary systems can be accessed. In this study, the dorsal root ganglion-ventral root (DRG-VR) complex was targeted with floating microelectrode arrays (FMAs) designed either to record from the VR or test stimulation paradigms in the DRG. Extensive characterization of the tissue response to these chronically implanted microelectrode arrays was performed to determine the reliability of these peripheral locations for interfacing applications. To accomplish these analyses, hematoxylin and eosin and Nissl/Luxol fast blue staining along with antibody-based stains [NF200 (axons), S100 (Schwann cells), vimentin (fibroblasts, endothelial cells, astrocytes), MAC387 (monocytes/macrophages), GLUT1 (glucose transport proteins)] were employed, regions of interest representing the entire area of the implanted array defined, and pixel-based image analyses specific for each stain utilized. Implanted roots were compared to the non-implanted (i.e., contralateral) roots from the same cohort of animals. The results indicate

that the inflammatory reaction elicited with array insertion is not significantly greater than what is observed in a control (i.e., non-implanted) spinal nerve. The absence of a significant immune response to these arrays suggests some level of immune privilege in the spinal nerve and bodes well for long-term applications. In addition, no significant decreases in neuronal density or myelination were observed in the area associated with the array indicating that both neuronal cell bodies and axonal projections are maintained. Observations related to the status of the blood-nerve barrier suggest it is preserved and/or reestablished at the chronic time points examined. Our data indicates that targeting the DRG-VR complex is a viable option and that the associated tissue response in this location is an opportunity to achieve the overall goal of a long-term, reliable interface with prosthetic limbs.

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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.18/HH32

**Topic:** E.05. Brain-Machine Interface

**Support:** DARPA/BTO/HAPTIX N66001-15-C-4018

**Title:** Effect of asymmetric, charge balanced stimuli on elicited compound neural action potentials

**Authors: *F. DELGADO**[1], A. KUNDU[2], E. PATRICK[3], S. W. CURRLIN[4], K. J. OTTO[3]
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**Abstract:** Nerve stimulations require careful optimization of waveform parameters, whether for sensory feedback or central neural network activation. Pulse width and amplitude are two parameters investigated often. Charge balanced symmetric pulses tend to appear most frequently in central nervous stimulation paradigms. While this convention tends to hold for peripheral nerve stimulation, this study assesses the possible utility of asymmetric pulse-width encoding in peripheral nerve stimulation. Toward this end, a series of asymmetric sequences were designed to determine what, if any, effect asymmetric stimuli have on compound neural action potentials (CNAPs).
Experiments were conducted in vivo, stimulating in the rat Tibial nerve and recording in the Tibial and Peroneal nerves. Stimulations were delivered via a microwire electrode with CNAPs captured via cuff electrodes downstream. The sequences were asymmetric in pulse-width and amplitude but were kept charge balanced. The stimuli were presented cathode leading first and

then followed by the reverse of the sequence with anode leading pulses. The effect of the interpulse period was not investigated in this study and therefore was fixed at zero. To expand the parameter space and investigate the role of asymmetry in the stimuli, six base stimuli amplitudes were delivered. The stimuli ranged logarithmically from 50 microamperes to 200 microamperes.
After stimuli delivery, the compound neural action potentials were sorted and averaged. From the data strip, stimulus artifact was removed from the leading edge and noise introduced from the muscle was removed from the trailing end. The remaining data strip was considered the contribution from neural activity. To determine the efficacy of each stimulus, the root mean square (RMS) of the signal was calculated. The RMS of the signal is proportional to the number of recruited fibers within a nerve fascicle; the RMS of individual stimuli were then compared against each other to determine which stimulus gave the highest recruitment value. Recent results have shown that varying the degree of asymmetry has had no significant effect on the RMS of recorded CNAPS.

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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.19/HH33

**Topic:** E.05. Brain-Machine Interface

**Title:** Optimal spatial and frequency parameters of subthalamic neurostimulation for the neural and kinematic signatures of gait impairment in freely moving Parkinson’s subjects

**Authors: *C. ANIDI**, J. O'DAY, M. F. AFZAL, J. SYRKIN-NIKOLAU, A. VELISAR, T. MARTIN, H. BRONTE-STEWART
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**Abstract: Objective**: Gait impairment and freezing of gait (FOG) are severe complications of Parkinson’s disease (PD) and are characterized by specific kinematic and subthalamic neural signatures. We investigated the effect of low versus high frequency STN deep brain stimulation (DBS) through the ventral versus more dorsal STN electrode(s) on synchronized neural and kinematic recordings in freely moving PD subjects.
**Methods**: 6 PD subjects (11 STNs), off-medication, performed a forward walking (FW) task, a stepping in place (SIP) task on dual force plates, and a FW turning and barrier course (TBC), during which synchronized local field potentials (LFPs) and kinematic data were recorded. Tasks were completed during NO, 60 Hz and 140 Hz DBS at a clinical equivalent voltage. STN LFPs

were recorded bilaterally from electrodes 0 - 2 and 8 - 10 of the left and right STN DBS leads (model 3389, Medtronic, Inc.) on to an investigational sensing neurostimulator (Activa® PC+S, Medtronic Inc., FDA-, IDE-, IRB-, and CA Medicare-approved) before and during DBS through electrode 1 and 9 respectively. During the SIP task, kinematic data was recorded during 60 and 140 Hz DBS on the most ventral electrodes at the same voltage as the more dorsal electrode paradigm. Kinematic data was recorded using wireless Opal® inertial measurement unit (IMU) sensors (APDM, Inc.). Angular velocity signals from IMUs on the lower legs were used to determine gait cycle duration, swing phase duration, and swing angular range. Angular velocity signals from the lumbar IMU were used to determine forward direction and delineate periods of straight walking and turning.
**Results**: 6 subjects (11 STNs) completed FW, SIP, and TBC while off stimulation and during 60 and 140 Hz DBS. STN DBS at 60 and 140 Hz decreased the number of freezing episodes (FEs) in freezers and attenuated beta band power compared to the off stimulation state. In all subjects, there were fewer FEs of shorter duration during 60 Hz compared 140 Hz DBS. Preliminary results from 3 subjects during the SIP task demonstrated greater improvement in both gait arrhythmicity and asymmetry during both frequencies of DBS on the most ventral electrodes when compared to the more dorsal electrode.
**Conclusions:** Low and high frequency STN DBS improved FOG and simultaneously attenuated beta band power. Preliminary analysis suggested that 60 Hz DBS was more efficacious and in the ventral STN region may be a better target than more dorsal STN regions to treat FOG in PD. Optimizing spatial and control policy parameters will be important for closed loop DBS systems.

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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.20/HH34

**Topic:** E.05. Brain-Machine Interface

**Title:** Subthalamic neural closed-loop deep brain stimulation in Parkinson's disease using patient specific functionally relevant frequency bands

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**Abstract: Objective**: Exaggerated neural synchrony in the beta band (13-30Hz) in the subthalamic nucleus (STN) is a pathophysiological marker in Parkinson’s disease (PD), the

attenuation of which is related to the improvement in bradykinesia. We compared the efficacy of neural closed-loop deep brain stimulation (NCL-DBS) for bradykinesia using patient-specific beta sub-bands that were more or less attenuated by deep brain stimulation compared to the off DBS state. **Methods**: To determine the upper and lower voltages for NCL-DBS and the beta band control variables, 6 akinetic-rigid consenting PD subjects (10 STNs), off-medication performed a repetitive wrist flexion-extension task (rWFE) during randomized presentations of 140Hz contralateral STN open loop (OL-)DBS at 0%, 25%, 50%, 75% and 100% of their maximum tolerable voltages. Synchronized wrist angular velocity and STN local field potentials (LFPs) were recorded during the task. Angular velocity was recorded using wearable gyroscopic sensors and LFPs were recorded from electrodes 0 -2 or 1 -3 of the DBS lead (model 3389, Medtronic, Inc) on to a sensing implanted neurostimulator (Activa®PC+S, FDA-, IDE-, IRB-, and CA Medicare-approved). LFP power spectral density identified two LFP bands between 8-30 Hz in each STN that were more or less attenuated during the voltage range used for NCL-DBS; these were used independently to drive NCL-DBS (Activa®PC+S and Nexus-D3/E system; Medtronic, Inc). **Results**: 6 PD subjects have completed WFE during randomized presentations of contralateral OL-DBS, 2 of whom have also completed a trial of 60 minutes of NCL-DBS driven by the beta sub-band that was maximally attenuated during OL-DBS. Preliminary results demonstrated that for each subject compared to off DBS, the root mean square angular velocity ($V_{rms}$) increased by 631% and 1692%; the coefficient of variation (CV) of $V_{rms}$ decreased (more regular) by 66% and 86%; the mean frequency of movement increased by 362% and 442%; and the CV of frequency decreased by 79% and 83% during NCL-DBS. $V_{rms}$ and frequency were greater on NCL-DBS compared to OL-DBS in both subjects. The total electrical energy delivered decreased by 43% and 63% during NCL-DBS as compared to their clinical OL-DBS.**Conclusions**: Neural closed loop STN DBS using LFP power in a patient specific, functionally relevant beta sub-band improved the velocity, frequency and regularity of progressive bradykinesia in akinetic rigid PD subjects and was more efficacious and efficient than their clinical open loop DBS. Further comparison of efficacy, side effect profile, and efficiency of patient specific NCL-DBS will be made with functionally irrelevant beta bands and with OL-DBS.

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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.21/HH35

**Topic:** E.05. Brain-Machine Interface

**Support:** NSF Grant DGE 1106400

**Title:** OMNI: A wireless,128-channel closed-loop neuromodulation device

**Authors: *A. ZHOU**[1], S. R. SANTACRUZ[1,2], B. C. JOHNSON[1,3], G. ALEXANDROV[1], A. MOIN[1], F. L. BURGHARDT[1], I. IZYUMIN[3], E. ALON[1], J. RABAEY[1], J. M. CARMENA[1,2], R. MULLER[1,3]
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**Abstract:** Closed-loop neuromodulation systems, which deliver therapeutic microstimulation based on the real-time neural state of the patient, aim to provide on-demand therapy and reduce side effects, while also extending battery life. These technologies must be able to simultaneously record neural signals, remove stimulus artifact from recorded data, and extract neural biomarkers and behavioral states to optimally and automatically deliver microstimulation. To address these needs we have developed OMNI, a wireless and autonomous neurotechnology for closed-loop neuromodulation and continuous, high-throughput streaming of neural data.
OMNI utilizes two custom 64-channel ASICs for recording and stimulation, whose outputs can be dynamically assigned to any of 128 electrode channels. The ASICs provide highly reconfigurable stimulation parameters and nearly artifact-free recording during stimulation, resulting in real-time closed-loop computation on local neural activity during stimulation. On-board computational components enable neural signal processing and closed-loop control algorithms, and wireless data communications allow for operation during natural behavior with 11+ hours of battery life.
OMNI has been deployed in a nonhuman primate (NHP) subject for closed-loop microstimulation during a manual-control delayed reach task. The device records local field potential (LFP) activity and determines when the NHP is performing different sub-stages of the task by thresholding the power in different frequency bands, with all computation done on-board. The reaction time is increased by delivering targeted microstimulation in dorsal premotor cortex (PMd) during the delay-hold periods of the task, prior to the onset of movement. The OMNI device was also used for overnight cortical and subcortical recording during free, natural behavior. The pilot NHP study demonstrates the comprehensive recording and closed-loop functionality of the OMNI device.

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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.22/HH36

**Topic:** E.05. Brain-Machine Interface

**Title:** An implantable brain-computer interface for investigation of closed-loop therapies

**Authors: *J. RICKERT**[1,2], F. KOHLER[1], C. STOLLE[1], T. STIEGLITZ[3,2], J. FISCHER[1], M. SCHUETTLER[1], C. GKOGKIDIS[4,3], X. WANG[3,4], M. GIERTHMÜHLEN[3], C. SCHEIWE[4], T. BALL[2,4]
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**Abstract:** In 1997, deep brain stimulation (DBS) was approved by the FDA for treatment of essential tremor. In the following decades neuromodulation of the CNS became a active field and was applied for treating different conditions. Similar to the technological progress of cardiac pacemakers, concepts were developed to adapt the stimulation to the patient's need, making the devices responsive. Today, two of these closed-loop devices are approved for clinical use, Medtronic Activa PC+S and Neuropace RNS. Both devices work with eight electrode contacts on the surface or deep inside the brain and permit delivery of electrical stimuli initiated, or modified in intensity, based on neural recordings. Here, we present a closed-loop device that overcomes current application limitation by increasing the electrode contact number, minimizing the closed-loop response time and transferring the closed-loop algorithms to a device outside the body, allowing maximum freedom for clinical research. The design is inspired by today's cochlear implants: The implant is wirelessly powered by a body-external transceiver. Cortical electrode arrays and DBS electrodes can be connected to the hermetically packaged implanted electronics. The device records synchronously from 32 electrode contacts at 1kS/s (16bit) at a pass band of 0.5 to 450Hz. Data are wirelessly streamed to the body-external transceiver, which is connected to a laptop-PC, running the control software. The software can send instructions to the implant to generate electrical stimuli of up to 6mA on each of the 32 electrode contacts. Typically, it takes some 10ms for closing the loop of recording and recording-based stimulation, strongly depended on the signal analysis and decision-taking algorithms used.
The system was implanted in sheep (approved by the Regierungspraesidium Freiburg, Germany and the Animal Ethics Committee of the University of Freiburg) to investigate long-term functionality and biological acceptance. Excellent robustness of the implanted hardware, good biological acceptance and stable recording signal quality could be demonstrated. We present the

latest results from the animal studies and technical improvements developed based on prior results. In conclusion, the implant system presented has the potential for researching closed-loop therapies for the central nervous system. The validations towards clearance for clinical studies are currently on the way.
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**Poster**

**498. Neurophysiology: Implanted Electrodes and Direct Interactions With Neurons - Stimulation and Closed-Loop**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 498.23/II1

**Topic:** E.05. Brain-Machine Interface

**Title:** Electrical brain stimulation causes patient to sing

**Authors: *A. C. CONNOLLY**[1], K. A. BUJARSKI[2], C. MARTIN[3], B. C. JOBST[2], D. W. ROBERTS[4]
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**Abstract:** Electrical brain stimulation (EBS) can occasionally cause overt behavioral responses in patients. Nearly all of those reported in the literature represent simple behaviors including lip-smacking, unintelligible vocalizations, changes in muscle tone, or reflexive uncontrolled muscle movements. Here we present a case of EBS of the right non-language dominant cingulate gyrus during functional brain mapping for epilepsy surgery which resulted in the singing of spoken language. Stimulation at a single pair of electrodes reliably caused the patient to involuntarily switch from speaking to singing whole phrases and sentences. This observation provides evidence that the cingulate gyrus is directly involved in motor control of singing. We discuss this finding in the broader context of cognitive neuroscience research on singing. We conclude that the automatic and involuntary nature of the EBS-induced singing behavior supports recent claims that the singing faculty in humans is phylogenetically ancient and is supported by dedicated neural circuitry.

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**Poster**

**499. Brain-Machine Interface: Sensory Systems**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 499.01/II2

**Topic:** E.05. Brain-Machine Interface

**Support:** DARPA Cooperative Agreement Number W911NF-15-2-0016

**Title:** Effect of stimulus parameters on perceived sensation and phantom limb pain during stimulation of cervical spinal cord and dorsal roots in upper-limb amputees

**Authors: *S. CHANDRASEKARAN**[1], A. C. NANIVADEKAR[2], A. I. KASHKOUSH[1], E. R. HELM[3], M. L. BONINGER[3], J. L. COLLINGER[1], R. A. GAUNT[4], L. E. FISHER[4]
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**Abstract:** Numerous studies indicate that sensory feedback could enhance the embodiment and ease of use of prosthetic limbs and potentially alleviate phantom limb pain (PLP). Electrical stimulation of the peripheral and central nervous system is the focus of extensive research as a means of providing this sensory feedback. In this study, we targeted stimulation to the dorsal spinal cord and roots (DSCR) to provide sensory feedback in upper-limb amputees. The DSCR provide a clear separation between the sensory and motor pathways, thereby avoiding any undesired concurrent activation of motor pathways that could contaminate a myoelectric interface. Also, the DSCR can be accessed through a minimally invasive surgical technique. Here, we present observations from human psychophysics experiments performed while stimulating the C5-C8 DSCR in two upper-limb amputees using FDA-approved spinal cord stimulation leads. Using percutaneous implantation techniques, we placed three 8 or 16-contact leads (Boston Scientific) in the lateral epidural space of the cervical spinal cord. Stimulation was delivered using a custom external stimulator for up to 4 weeks, after which the electrodes were removed. Information regarding the modality, location, and intensity of perceived sensations was provided by the subject using a structured reporting system. We found that stimulation frequency had a stronger effect than stimulus amplitude on the intensity of perceived sensations and often, dictated the perceptual modality of the sensation. However, across different electrodes, changes in intensity or perceived sensation area were not consistently monotonic with respect to changes in stimulus parameters. Using multivariate analyses, we determined which stimulus parameters could most reliably predict the intensity of a perceived sensation. This information will be useful in scaling the perceived intensity in accordance with sensor information during closed-loop tasks. To assess PLP, we asked the subject to report the PLP intensity after every trial of stimulation. Also, the McGill Pain Questionnaire (MPQ) was administered once before implantation, weekly during the stimulation phase and again one month after explantation. The

subjects reported a transient increase in PLP that was correlated in intensity and likelihood with stimulation amplitude and pulse width respectively, whenever sensory stimulation was delivered. However, in contrast, we observed a clinically significant reduction (>5 points) in PLP from baseline over the 4 weeks of stimulation as determined by the MPQ. This time-dependent modulation of PLP by sensory feedback will be explored in future experiments.

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**Poster**

**499. Brain-Machine Interface: Sensory Systems**

**Location:** Halls A-C

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**Topic:** E.05. Brain-Machine Interface

**Support:** Parkinson Schweiz foundation

European Union project Neuwalk

European Union project Walk Again

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SNSF Sinergia program

SNSF Sino-Swiss Science and Technology Cooperation program

SNSF project SpineRepair

**Title:** A wireless brain-spine interface that alleviates gait deficits of Parkinson's disease

**Authors: *T. MILEKOVIC**[1,2], F. RASCHELLA[3], G. SCHIAVONE[4], Y. JIANZHONG[5,6], W. D. KO[5,6], L. QIN[5,6], C. QIN[5], M. CAPOGROSSO[7,2], S. P. LACOUR[4], J. BLOCH[8], S. MICERA[3,9], E. BEZARD[10,5,6], G. COURTINE[2,8]
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**Abstract:** Levodopa and deep brain stimulation alleviate most of the symptoms associated with Parkinson's disease. However, axial gait disorders are less responsive to these treatments. These deficits include short and slow steps, balance deficits and freezing of gait that involves episodes during which the affected persons are unable to initiate locomotion. Over the past decade, we have established a mechanistic and technological framework that guided the design of electrical spinal cord stimulation protocols engaging extensor and flexor muscle groups. We created an interface between the leg motor cortex activity and these spatially selective stimulation protocols, so as to engineer a brain-spine interface - a neuroprosthetic system that reinforced intended movements. As early as 6 days after spinal cord injury, this brain-spine interface restored weight-bearing locomotor movements of the paralyzed leg in nonhuman primates. Here, we show that the brain-spine interface effectively alleviates axial gait deficits observed in Parkinson's disease. These experiments were conducted in MPTP-treated Rhesus macaque monkeys, which is the gold standard model of Parkinson's disease symptomatology. After MPTP treatment, a rhesus macaque was implanted with the wireless brain-spine interface. Brain recordings of the left and right leg motor cortex were used to detect neural states related to flexion and extension movements of both legs while the animal walked freely overground or over a horizontal ladder. The detection of these gait events controlled an implanted pulse generator that delivered electrical stimulation through two e-dura (dura mater like) electrode array implants, which covered the dorsal aspects of the lumbar and sacral spinal cord. The brain-spine interface instantly improved gait execution when compared to non-stimulation condition. These improvements manifested in increased speed along the corridor and the ladder, and the absence of falls on the horizontal ladder, which contrasted to the frequent misplacements that occurred without stimulation. These preliminary results open promising avenues for evaluating the ability of the wireless brain-spine interface to alleviate gait deficits in people with Parkinson's disease.

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**Poster**

**499. Brain-Machine Interface: Sensory Systems**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 499.03/II4

**Topic:** E.05. Brain-Machine Interface

**Support:** NIH R01 NS095251

Duke Compute Cluster

**Title:** Model-based design of optimal spatiotemporal patterns of intracortical microstimulation for prosthetic sensation

**Authors: *K. KUMARAVELU**[1], T. TOMLINSON[2], T. CALLIER[3], S. J. BENSMAIA[3], L. E. MILLER[2,4,5], W. M. GRILL[1,6,7,8]
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**Abstract:** Loss of touch and proprioception, e.g., due to spinal cord injury, causes significant movement deficits, and the absence of sensory feedback limits the function of prosthetic devices. We are developing a biomimetic approach to evoke sensory percepts through intracortical microstimulation (ICMS) of somatosensory cortex (S1). One of the key challenges of the biomimetic approach is to determine the spatiotemporal pattern of multi-channel ICMS that results in neural responses that mimic those evoked by naturalistic sensory inputs. However, the response to multi-channel ICMS is not expected to be the superposition of responses evoked by individual channel stimulation due to strong nonlinear interactions. This results in an exceedingly large stimulus parameter space that cannot be searched by brute force, and we developed a systematic approach to design biomimetic patterns of ICMS.
We recorded multiunit activity (SPIKES) from area 2 of S1 in two rhesus macaques using a 96 channel multi-electrode array during a center-out reach task. The task spanned eight reach directions in a 2D space and the hand position ($PHYS_{prop}$) was continuously tracked. We also recorded SPIKES from S1 area 1 in a rhesus macaque during application of indentations ($PHYS_{tact}$) of varying amplitudes onto digits D3 and D4.
We implemented a computational model of a cortical hypercolumn (*slab* model) comprising 100 modules arranged in a 10*10 grid. Each module consisted of an anatomically realistic, layer-specific cortical minicolumn, following an existing model of multi-compartment cortical neurons (Traub et al., 2005). The layer-4 neurons were extracted from the *slab* model, and a simplified *sheet* model was used with a genetic algorithm to design spatiotemporal patterns of ICMS

(STIM). We identified optimal STIM patterns such that model-based responses (EVOKED) approximated the measured SPIKES. We tested the performance of sheet model-optimized STIM on the more complex slab model. The slab model EVOKED responses matched SPIKES for neurons <100 um from the electrode tip.
Finally, we developed a mapping function between PHYS and STIM – the sensory encoder to be integrated into a neuroprosthetic device – by training a recurrent neural network (RNN). The RNN was cross-validated using PHYS that were not included in training and evaluated the output STIM on the sheet model. The RNN-predicted STIM generalized well to untrained $PHYS_{prop}$ reach trials, with the degree of similarity between SPIKES and EVOKED being comparable to trial-trial variability between SPIKES.
This framework enables an encoder to evoke biomimetic patterns of neural activity and thereby naturalistic sensory percepts.

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**Poster**

**499. Brain-Machine Interface: Sensory Systems**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 499.04/II5

**Topic:** E.05. Brain-Machine Interface

**Title:** Sensory feedback driven by intraneural stimulation allows amputees to reduce energy consume during walking and decreases phantom limb pain

**Authors: *F. M. PETRINI**[1], G. VALLE[2], F. BARBERI[1], D. BORTOLOTTI[1], P. CVANCARA[3], A. HIAIRRASSARY[4], D. GUIRAUD[4], J.-L. DIVOUX[5], A. LESIC[6], T. STIEGLITZ[3], S. MICERA[2], S. RASPOPOVIC[1], M. BUMBASIREVIC[6]
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**Abstract:** Leg amputees do not have natural sensory information from commercial prostheses. As a consequence, amputees risk falls, and lose confidence in the prosthesis, so that patients exert counterbalancing movements with the sound leg increasing metabolic costs, and leading to catastrophic events as heart failures. Also, because of the lack of sensory feedback, 50 to 80% of amputees report phantom pain from the missing leg. Some efforts to restore sensory feedback in lower limb amputees have been conducted with non-invasive technologies, but they failed in addressing these problems. In this work we developed the first prosthetic leg, which restores sensory feedback to amputees by means of implanted intraneural electrodes, in order to reduce metabolic costs during walking and to decrease phantom limb pain. Two transfemoral amputees

underwent the implant of 4 TIME electrodes in the tibial nerve for three months. The response of the subjects to the nerve stimulation was characterized during the whole course of the study. We showed that natural sensations of touch and muscle contractions could be elicited on the phantom leg on the whole area of innervation of the tibial nerve. A commercial prosthetic leg with an encoder embedded in the knee was equipped with a custom made sensorized sole, giving pressure information from 7 positions of the foot sole. The readout of these sensors was used to drive wirelessly the stimulation of 4 active sites, eliciting natural touch under the foot sole and calf contraction, intuitively interpreted by the subject as knee flexion. The subjects were asked to walk with the prosthesis restoring sensory feedback at increasing velocity on a treadmill for 8 minutes. Then they were asked to walk outdoor for 6 minutes at a self-assessed speed on a fixed path on send and grass. These trials were repeated with and without restored sensory feedback, while the metabolic costs were measured. Finally, the subjects underwent sessions of 10-minutes continuous monopolar biphasic square stimulation. The volunteers replied to standard pain questionnaires before and after the stimulation. Remarkably, we measured significantly reduced metabolic costs both indoor and outdoor when the subjects walked with the prosthesis restoring sensory feedback. Furthermore, the subjects reported a significant decrease of phantom pain after the provision of 10 minutes stimulation. These results show that natural invasive sensory feedback restored by means of intraneural electrodes successfully addresses current limitations of prosthetic devices, opening the way for a dramatic improvement of amputees' life.

**Disclosures:** **F.M. Petrini:** None. **G. Valle:** None. **F. Barberi:** None. **D. Bortolotti:** None. **P. Cvancara:** None. **A. Hiairrassary:** None. **D. Guiraud:** None. **J. Divoux:** None. **A. Lesic:** None. **T. Stieglitz:** None. **S. Micera:** None. **S. Raspopovic:** None. **M. Bumbasirevic:** None.

**Poster**

**499. Brain-Machine Interface: Sensory Systems**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 499.05/II6

**Topic:** E.05. Brain-Machine Interface

**Title:** A comparison between encoding strategies for restoring sensory feedback in a bidirectional hand prosthesis

**Authors: *G. VALLE**[1], I. STRAUSS[1], F. M. PETRINI[2], G. GRANATA[3], R. DI IORIO[3], P. CVANCARA[4], M. MULLER[4], M. BARBARO[5], L. RAFFO[5], T. STIEGLITZ[4], S. RASPOPOVIC[2], P. M. ROSSINI[3], S. MICERA[2,1]
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**Abstract:** In the last years several research groups have demonstrated that nerve stimulation by implantable peripheral nerve interfaces can be reliably used to restore sensory feedback to upper limb amputees. It has been shown that this improves the performance of controlling hand prostheses. Different strategies to transduce the readout of hand prostheses sensors have been tested. Recently, it has been demonstrated that the charge and frequency of neural stimulation have a linear relationship with the intensity of the elicited sensation. Here, we developed a bidirectional hand prosthesis, in which the readout of force sensors in the hand is linearly related or to the charge or to the frequency of intraneural stimulation. This was done in order to verify whether one approach produced better than the other in improving motor control performance. We implanted the median and ulnar nerve of a transradial amputee, above the elbow, with 4 TIME electrodes. We identified the active sites able to elicit the sensation of touch/pressure in the median and ulnar areas of the hand. The subject controlled the hand prosthesis using the residual arm muscles, whose activation was recorded by surface EMG electrodes. The acquired signals were pre-processed and fed to a KNN to classify, within 100 ms delay, the intention to open, close and not move the hand. The subject blind-folded and acoustically isolated was engaged in 4 tasks from the literature: force control, object location, compliance and shape recognition. In the first one, the subject was asked to control the force level he could exert by the prosthesis on a pressure sensor. 3 levels of force were required either in a casual order or in a ramp fashion from the minimum to the maximum one and back. In object location the subject had to recognize if an object was placed in the ulnar or median portion of the hand or in both. Finally, the volunteer had to distinguish among 3 objects of different compliance or shape. The subject successfully performed object location, compliance and shape recognition, with both charge and frequency modulation. During the force control task, instead, while the volunteer was perfectly capable of controlling three randomly required force levels with both stimulation strategies, she managed to execute the ramp only by means of charge modulation. When the frequency was modulated, indeed, it was impossible for the subject to control the force level from the maximum to the minimum one. This suggests that the intensity of sensations elicited by neural stimulation decays rapidly over time when high frequency is used, making charge modulation strategy a more reliable to exploit in bidirectional prostheses development.

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**Poster**

**499. Brain-Machine Interface: Sensory Systems**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 499.06/II7

**Topic:** E.05. Brain-Machine Interface

**Support:** NIH Grant NS096064

**Title:** Learning object discrimination using electrotactile feedback

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**Abstract:** A variety of bioengineering systems are being developed to restore tactile sensations in individuals who have lost somatosensory feedback because of spinal cord injury, stroke, or amputation. These systems typically detect tactile force with sensors placed on an insensate hand (or prosthetic hand in the case of amputees) and deliver touch information by electrically or mechanically stimulating sensate skin above the site of injury. Successful object manipulation, however, also requires proprioceptive feedback representing the configuration and movements of the hand and digits. Therefore, we developed a simple system that simultaneously provides information about tactile grip force and hand aperture using current amplitude-modulated electrotactile feedback. We evaluated the utility of this system by testing the ability of five healthy human subjects to distinguish among 27 objects of varying sizes, weights, and compliances based entirely on electrotactile feedback arising from grip-force and hand-aperture sensors placed on the hand of an experimenter (not visible to the subject) grasping and lifting the test objects. We were also interested to determine the degree to which subjects could learn to use such feedback when tested over multiple sessions. The average percentage correct identifications on day 1 (25.9 ± 6.2% correct) was well above chance (3.7%) and increased significantly with training to 46.2 ± 13.6% on day 5. These results suggest that simple, non-invasive methods can provide useful multisensory feedback that might prove beneficial in improving the control over prosthetic limbs.

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**Poster**

**499. Brain-Machine Interface: Sensory Systems**

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**Program#/Poster#:** 499.07/II8

**Topic:** E.05. Brain-Machine Interface

**Support:** FRM DBS20140930785

ANR-16-CE19-0005

ANR-15-CE19-0006

**Title:** Decoding articulatory representation of speech from cortical recordings: A preliminary study

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**Abstract:** Brain-Computer Interfaces (BCIs) usually propose typing strategies to restore communication for paralyzed and aphasic people. A more natural way would be to directly control a speech synthesizer through a BCI. Neural activity from the speech motor cortex has been shown to be correlated to the articulatory features of produced speech. Thus, a BCI using neural activity from the speech motor cortex might benefit from decoding an articulatory representation of speech rather than an acoustic one. Such an articulatory representation could then be converted to an audible speech signal using an articulatory-based speech synthesizer. In a previous work, we built such a synthesizer and showed that it could produce intelligible speech from movements of the jaw, tongue, lips and velum, in real-time closed-loop condition. In this preliminary study, we recorded neural activity from several subjects undergoing awake surgery for a tumor removal using both electrocorticographic or intracortical micro-electrode arrays, during production of overt or covert speech. We then investigated the decoding of articulatory trajectories from the recorded neural activity, which was compared to a direct decoding of acoustic features. To perform this comparison, decoded articulatory trajectories were converted to acoustic features using our articulatory-based speech synthesizer.

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**Poster**

**499. Brain-Machine Interface: Sensory Systems**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 499.08/II9

**Topic:** E.05. Brain-Machine Interface

**Support:** JSPS Grant 15K20258

**Title:** The color of the phosphenes elicited by artificial vision by direct optic nerve electrical stimulation (AV-DONE)

**Authors: *K. NISHIDA**[1,2], H. SAKAGUCHI[1], M. KAMEI[3], Y. TERASAWA[4], T. FUJIKADO[1], K. NISHIDA[1]
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**Abstract:** Objective: To analyze the color of the phosphenes elicited by AV-DONE.
Methods: The patient was a 44-year-old man with autosomal-recessive RP and bare light

perception. The patient had no other ocular diseases or systemic disorders that could have caused the visual loss. After a standard three-port pars plana vitrectomy, the electrode device with wires was inserted into the vitreous cavity through the silicon trocar. Then, the electrode tips were inserted into the optic disc. Next day biphasic, cathodic-phase-first, electrical pulse trains with a 1-s total duration were applied between one of the stimulation electrodes and the reference electrode. The duration of the stimulus pulses was 0.25 ms/phase, and the frequency was 320 Hz. The patient was questioned about perception of the phosphenes, their clock position (1 to 12 o'clock), and the color of the phosphenes.
Results: The patient identified electrically induced phosphenes through six of the seven stimulation. The phosphenes was distributed focally in the visual field. The average central position of the phosphenes differed for each electrode. The colors of phosphenes were red (13%), yellow (9%), white (8%), blue (31%), pink (19%) and green (20%).
Conclusion: The phosphenes elicited by AV-DONE have several variations of the color. With effective use of the phosphenes, AV-DONE could provide the blind patients with useful information.
The color of the phosphenes elicited by Artificial Vision by Direct Optic Nerve Electrical stimulation (AV-DONE).

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**Poster**

**499. Brain-Machine Interface: Sensory Systems**

**Location:** Halls A-C

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**Program#/Poster#:** 499.09/II10

**Topic:** E.05. Brain-Machine Interface

**Support:** MTEC Grant FP0000 8807

**Title:** Evoking visual percepts via epicortical microstimulation of primary visual cortex

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**Abstract:** Electrical stimulation of primary visual cortex (V1) is a potential means to restore limited vision to those with profound blindness. Early studies using epicortical macroelectrodes demonstrated this technique could evoke phosphenes and simple visual patterns. However, high levels of current were required, yielding unnatural sensations and a concern for initiation of seizure activity. The use of intracortical microelectrodes reduced the level of current needed to

evoke visual percepts, but presents other challenges. Since intracortical microelectrodes are inserted into the parenchyma and violate the blood-brain barrier, their use may comparatively increase tissue response and reduce longevity. With a large portion of V1 residing in the sagittal fissure, the complex geometry of intracortical arrays complicates surgical implantation for more peripheral visual field representation. Epicortical microelectrodes may improve longevity and visual field accessibility. Provided that epicortical microelectrodes can evoke visual percepts at lower current levels than macroelectrodes, they may provide an effective route to restore limited vison.
A 46-channel epicortical array (Second Sight Medical Products) with concentric rings was implanted in two rhesus macaques (macaca mulatta), NHP0 and NHP1, to determine what electrode diameters can evoke visual percepts and how thresholds change with diameter. The rings create diameters of .2, .75, 1.5, and 2 mm. Each array was placed in the sagittal fissure facing right hemisphere, with the caudal-most point of the array in close approximation to the pole, superior to the calcarine. Subjects were trained to respond to small flashes of light on a CRT monitor by using the left hand to indicate perception and the right hand to indicate no perception. Electrical stimulation was then applied to individual electrodes. Tissue damage was assessed by functional changes in the subjects' perception of photic stimuli.
Both subjects responded as perceiving a visual percept with currents in the range of 300-900µA applied to 200µm diameter electrodes. Psychometric data for NHP1 places the average 50% detection rate during stimulation on 200µm electrodes at 375.5µA. Following 12 months of daily stimulation NHP0 showed no significant changes in photic perception. Electrode impedances remained consistent during the 18 months NHP0 was implanted.
Epicortical microelectrodes can evoke visual percepts at lower levels than epicortical macroelectrodes. Percpts can be evoked several months post implant with consistent thresholds and steady electrode impedances, suggesting array stability and consistent charge delivery over time.

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**Poster**

**499. Brain-Machine Interface: Sensory Systems**

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**Topic:** E.05. Brain-Machine Interface

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KAKENHI 15H05880

**Title:** An SSVEP-based brain-computer interface applied to patients with persistent vegetative state

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**Abstract:** Patients who represent no evidence of awareness of self and environment, and no evidence of volitional response to passive stimulus like an auditory, visual, and tactile have been diagnosed as persistent vegetative state (PVS, Plum and Posner, 1972), or recently as unresponsive wakefulness syndrome (UWS, Laureys, et al., 2010). Recent neuroimaging studies have suggested that some of the patients who diagnosed as PVS/UWS may be able to modulate their thoughts voluntarily (Monti, et al., 2010, Cruse, et al., 2011); however, brain-computer interfaces (BCIs) applied to patients with PVS/UWS have not been successful (Lule, et al., 2013, Pan, et al., 2014). In this study, we applied a steady-state visual evoked potential (SSVEP)-based BCI (Sakurada, et al., 2015) to patients with PVS/UWS. Four patients with PVS/UWS participated in this experiment (1 male, mean: 45.5 years old, JFK Coma Recovery Scale-Revised (CRS-R) mean: 6, ranged 5-7). Following verbal instructions, the participants were asked to attend to or ignore a green/blue flicker, which elicited SSVEPs from the occipital cortex (an attention/ignorance task). We calculated power spectral density (PSD) of target frequency to evaluate their classification accuracy. When asked to attend to, if the PSD of the frequency of the flickering light-emitting diode (LED) crossed over the threshold for 4 sec, the response was recognized as a correct answer. When asked to ignore, if the PSD was kept below the threshold for 30 sec, the response was accepted as a correct answer. Online accuracies were evaluated. Online feedback regarding the task performance was verbally delivered to the participants. In the attention/ignorance task, mean accuracy was 66.3% (n=4, total 90 trials). The mean accuracies were below 70% in 3 out of 4 patients, but a patient (female, 20 years old) achieved a reliable accuracy (mean 80%, 30 trials).The results showed that a patient who diagnosed as PVS/UWS was able to operate our SSVEP-based BCI system in a reliable accuracy, and suggested that some of the patients with PVS/UWS might be able to modulate their thoughts voluntarily and our system might detect volitional responses from the patient group.

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**Poster**

**500. CPGs: Non-Mammalian**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 500.01/II12

**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** National Natural Science Foundation of China (Grants 31671097, 31371104)

National Institutes of Health (Grant NS066587, NS070583, and MH051393)

**Title:** Motoneuronal and interneuronal control of rolling waves that mediate *Aplysia* locomotion

**Authors: *K. YU**[1], D.-D. LIU[1], S.-Y. YIN[1], G. ZHANG[1], W.-D. YUAN[1], E. C. CROPPER[2], K. R. WEISS[2], J. JING[1,2]
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**Abstract:** Rolling waves are rhythmic activity that propagates from one location to another, and can mediate some forms of vertebrate and invertebrate locomotion. Here, we study *Aplysia* locomotion, which is mediated by pedal rolling waves propagating from front to back, and seek to characterize the locomotor circuit. We have identified a cluster of ~20 P1 root neurons on the ventral surface of the pedal ganglion that exhibit different activity phases during fictive locomotion elicited by stimulation of nerve P9 or command interneurons CC9-10. A majority of these neurons are motoneurons as they project their axons to the periphery through pedal nerves P1, P7, P8, P9, and can elicit contraction of foot muscles when stimulated. Electrical coupling between motoneurons that are active in a similar phase may contribute to the generation of different activity phases in rolling waves.
With the exception of cerebral C cluster interneurons that activate locomotor programs (e.g., CC9/10) (Fredman and Jahan-Parwar 1983, Jing et al 2008), few interneurons involved in the control of locomotion have been identified. Here, we describe several novel interneurons located in both pedal and cerebral ganglia. On the ventral surface of the pedal ganglion, there are two major classes of interneurons. All have processes that are in close contact with the P1 root neuronal cluster. However, axon projections patterns differ. One class of interneurons projects their axons in a medio-antero-lateral circle within the ipsilateral pedal ganglion. These neurons are rhythmically active during fictive locomotion and can speed up the locomotor rhythm. The second class of interneurons projects to the contralateral pedal ganglion (via the pedal commissure). These interneurons can either speed up or slow down the locomotor rhythm. Moreover, one of the second class of interneurons elicits monosynaptic EPSPs on a P1 root cluster motoneuron in the contralateral pedal ganglion through axo-dendritic electrical coupling. This interneuron does not speed up the locomotor rhythm. On the dorsal surface of the cerebral ganglion, a D cluster interneuron projects its axon to the contralateral pedal ganglion through the

contralateral cerebral-pedal connective (CPC). This neuron is rhythmically active, and can drive a locomotor rhythm, although not as effectively as CC9-10. An E cluster interneuron projects its axon to the ipsilateral pedal ganglion through the ipsilateral CPC, and can slow down the locomotor rhythm. Thus, we identified a number of interneurons that may function as a part of the central pattern generator of the locomotor rhythm. Alternatively they may function as rhythm drivers or modulators.

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**Poster**

**500. CPGs: Non-Mammalian**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 500.02/II13

**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** DFG SM206/3-1

**Title:** Morphological and physiological analysis of a coordinating circuit

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**Abstract:** During swimming the four paired swimmerets of crayfish's abdomen are coordinated in an anteriorly proceeding metachronal wave with a phase lag of ≈ 25% between each segment. Each swimmeret is innervated by local interneurons of the central pattern generator (CPG) and motor neurons. The intersegmental coordination of the CPGs is achieved by three neurons located in each hemisegment forming a coordinating circuit. One ascending ($ASC_E$) and one descending (DSC) coordinating neuron encode the information about the status of their home module and project it to other ganglia. A nonspiking neuron, Commissural Interneuron 1 (ComInt1), decodes this information transmitted by three coordinating neurons with a gradient of synaptic strength, where the biggest EPSP is always elicited by the neighboring $ASC_E$, the intermediate by the neighboring DSC and the smallest by the coordinating neuron which is the farthest away. Firstly we investigated how the gradient of synaptic strength in ComInt1 is achieved? We hypothesized that the different sized EPSPs are due to differences in the synaptic contacts between ComInt1 and the three coordinating neurons. Therefore single coordinating neurons were filled with fluorescent dye and the synapses of the coordinating neurons on ComInt1 were marked immunohistochemically with Anti-Synapsin. Dorsally at the midline, where ComInt1 has one ascending and descending dendritic branch and the axons of the coordinating neurons pass through the other ganglia, we identified synapses of the coordinating

neurons by colocalized presynaptic boutons with the aborizations of the axon of intracellular stained coordinating axons. We could calculate areas of colocalization which correspond so far to the three distinct sizes of EPSPs in ComInt1. Secondly we investigated how ComInt1 decodes the information of the three coordinating neurons and how it is integrated into the own CPG? Therefore we recorded intracellularly from ComInt1 and changed the excitation level by bath application of different carbachol (CCh; cholinergic agonist) or edrophonium chloride (EdCl; acetylcholine esterase inhibitor) concentrations. To investigate direct and indirect actions of the drugs we measured input resistance ($R_{in}$) in an intact network and in the isolated neuron. $R_{in}$ did not change or increased with higher CCh concentrations, but decreased with increased EdCl concentration. CCh and EdCl did also influence the membrane potential, EPSP amplitude and membrane oscillation of ComInt1, but in an unpredictable way. However we suggest that the decoding of coordinating information is due to the effect of intrinsic modulation and externally applied excitation levels.

**Disclosures: F. Blumenthal:** None. **C.R. Smarandache-Wellmann:** None.

**Poster**

**500. CPGs: Non-Mammalian**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 500.03/II14

**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** DFG SM 206/3-1

UoC ZUK 81/1

**Title:** Command-like modulation of motor neurons and interneurons

**Authors: *F. CLOTTEN**, C. SMARANDACHE-WELLMANN
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**Abstract:** Locomotion is utilized in a wide range of behavioral contexts. Thus, the evoked motor output needs to be adapted to specific requirements, i.e. initiated or terminated, or modulated in timing or strength. The swimmeret system of the crayfish is an easily accessible model for studying locomotion and both excitatory and inhibitory ‘command neurons’ modulating the swimmeret output were described. However, so far no information is available about the input these neurons receive or their neural targets within the swimmeret system.
In this study separated axon bundles in the connectives of the abdominal nerve cord were stimulated electrically. Histological identification of the stimulation sides revealed that the locations of the stimulated axon bundles were consistent with previously described locations of excitatory and inhibitory ‘command neurons’. Stimulations induced, terminated, and enhanced

rhythmic activity, indicating stimulation of these command-like neurons.
To understand where the descending command-like input arises and where it is propagated within the ventral nerve cord (VNC) electrical stimulations at the level of the commissural connectives were performed. Comparable stimulation effects were observed and stimulus-evoked activity was recorded extracellularly at the most posterior portion of the VNC. These results give evidence that command-like input acting on the swimmeret system originates from high-order neural centers and is propagated throughout the entire VNC.
Both the swimmeret motor neurons (MN) and presynaptic interneurons of the pattern-generating micro-circuits are possible targets of the command-like neurons within the swimmeret system. Intracellular recordings during sub-threshold stimulations revealed a depolarizing effect on the membrane potential of MNs and activation of the CPGs. In addition, persistent swimmeret activity could be modulated by electrical stimulation, i.e. period decreased and power stroke bursts were strengthened. These results give evidence that both the MNs and CPGs are targeted by the command-like neurons.
The question of neuronal targets of the command-like input is associated with the question of potential neurotransmitters. Proctolin initiates and octopamine terminates rhythmic activity within the swimmeret system and evidence is given that these effects are due to release of these chemicals by command-like neurons. In this study, inhibitory stimulation effects, i.e. termination of rhythmic activity, were abolished by bath application of an octopamine antagonist, suggesting that inhibitory command-like neurons use octopamine as a neurotransmitter.

**Disclosures: F. Clotten:** None. **C. Smarandache-Wellmann:** None.

**Poster**

**500. CPGs: Non-Mammalian**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 500.04/II15

**Topic:** E.07. Rhythmic Motor Pattern Generation

**Title:** Dynamics of coordinated nerve-muscle-body-environment interaction in crustacean swimming

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**Abstract:** Effective locomotion arises from the integration of central neural circuits, muscle dynamics, mechanical interaction with the environment and sensory feedback. In mammals and arthropods that walk and swim using limbs, the movements of different limbs must be synchronized, and the phases and forces of each limb's movements must be adapted to changes in behavioral requirements. How do their nervous systems do it? The complexity of these

elements and their interactions, however, has impeded our understanding of these mechanisms at both cellular and system levels. The crustacean swimmeret system is one of the very few locomotor systems in which both the key neurons in the central pattern generating circuit and the topology of the coordinating synaptic network have been clearly identified. This makes possible a biophysical model of coordinated nerve-muscle-body-environment interaction that includes not only the key neural module and their synaptic connectivity but also a realistic musculoskeletal periphery that interacts with the external 3D fluid environment with sensory pathways returning to the central neural modules. Using mathematical modeling and analysis to guide neurophysiological experiments, and experimental results to constrain development of our model, we aim (1) to exploit features of the coordinating circuit to test predictions of requirements for stable metachronal coordination in the presence of proprioceptive input, (2) to quantify the role of proprioceptive feedback on the oscillations of individual modules, and (3) to construct a biophysically-detailed model of nerve-muscle-body-environment interaction, in which the 3D fluid environment provides feedback to the central neural circuit via proprioceptive pathways to individual neurons.

**Disclosures: C. Zhang:** None. **C.R. Smarandache-Wellmann:** None.

**Poster**

**500. CPGs: Non-Mammalian**

**Location:** Halls A-C

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**Program#/Poster#:** 500.05/II16

**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** DFG, RTG 1960

**Title:** Characterization of postinhibitory rebound in spiking and nonspiking neurons in a chain of coupled oscillators

**Authors: *L. SCHLAEGER**, C. R. SMARANDACHE-WELLMANN
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**Abstract:** Postinhibitory rebound (PIR) is one of several membrane properties that play an important role in producing rhythmic neuronal activities, by depolarizing following a phase of inhibition. We investigate this property in identified neurons of the swimmeret system. These neurons are characterized by membrane potential oscillations and account for the well coordinated generation of power- and return stroke movements of four pairs of pleopodes (swimmerets) at the abdomen of crayfish. To investigate this we isolated the abdominal nervous system and performed current clamp recordings with sharp electrodes at the dendritic aborizations of the neurons. To induce a PIR, hyperpolarizing current pulses at different holding potentials and with different amplitudes were applied. All neurons that are known to receive

inhibitory synaptic input possessed the ability to produce a PIR, which was accompanied by a small sag potential during the hyperpolarization. These are the neurons of the central pattern generator (CPG), IPS and IRS, the coordinating neurons, $ASC_E$ and DSC and the motor neurons PS and RS. The one neuron in the swimmeret system that is characterized solely by excitatory synaptic input, ComInt1, did not show the ability to produce a PIR, nor a sag potential. I could detect major differences in the PIR responses between the nonspiking CPG neurons and the spiking neurons $ASC_E$, DSC, PS and RS. At more depolarized holding potentials the spiking neurons showed a stronger PIR than at more hyperpolarized holding potentials. Contrary effects to a change in holding potential could be observed when inducing a PIR in one type of the nonspiking CPG neurons.In order to explain these contrasting we investigated the ionic basis of the PIR responses. Different ionic currents can account for the generation of a PIR. In other system the hyperpolarization activated cation current ($I_H$) or the L-type calcium current ($I_{CaL}$) were both shown to be key currents for this property. The L-type calcium channel antagonist nifedipine increased the PIR response in the spiking neurons while there was no effect on PIR in the CPG neurons. In both neuron groups the subsequent application of the H-current blocker ZD7288 almost completely suppressed all PIR responses. These results suggest that PIR is an essential mechanism for most of the neurons in the swimmeret system to generate membrane potential oscillations. Furthermore it seems that $I_{CaL}$ and $I_H$ play different roles for the generation of this response in spiking and nonspiking neurons which could account for the observed differences in the evoked PIR at different holding potentials.

**Disclosures: L. Schlaeger:** None. **C.R. Smarandache-Wellmann:** None.

**Poster**

**500. CPGs: Non-Mammalian**

**Location:** Halls A-C

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**Program#/Poster#:** 500.06/II17

**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** DFG SM206/3-1

UoC Advanced Research Grant

**Title:** Stability of a coordinated circuit during temperature perturbations

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**Abstract:** Temperature is a global perturbation, which influences biophysical parameters within neural circuits of animals. The crayfish's swimmeret system is an excellent model to test if the

coordination of distributed neural oscillators is robust against temperature changes. Swimmerets are four pairs of limbs attached to the abdomen, and are used for forward swimming. They are controlled and innervated by four of six abdominal ganglia. In each hemiganglion a neuronal circuit drives motor neurons which activate the limbs in alternating cycles of power-stroke (PS) and return-stroke movement. An identified coordinating circuit, consisting of two coordinating neurons and one commissural neuron (ComInt1), synchronizes these central pattern generators, so that a metachronal wave is present where the last segment starts with the PS activity and the anterior modules follow with a latency of approximately 20 to 25%.
To answer our question we used crayfish which were acclimated at three different temperatures: cold (4°C), intermediate (14°C) and warm (25°C). All experiments were done on the isolated nervous system with extracellular recordings of all motor nerves responsible for swimmeret movements and the two coordinating neurons. Additionally the activity of ComInt1 was recorded intracellularly. Saline with temperatures between 4°C to 35°C was perfused over the nerve cord. Independent of acclimation condition the period of the rhythm and PS burst duration decreased linearly with increased temperature. Duty-cycle was variable towards temperature changes. However, in all experiments the coordinated pattern of PS bursts from segment to segment remained stable, even if the optimum for a stable rhythm was shifted towards the acclimation temperature. Whereas a parabolic correlation was found for the duty cycle, spikes per burst and the interspike frequency of the coordinating neurons of intermediate acclimated animals towards temperature fluctuations. Additionally, corresponding to a faster rhythm frequency of the system the latency of EPSPs elicited by $ASC_E$ respectively DSC spikes in ComInt1 also decreased with rising temperatures. Independent of the acclimation temperature crayfish responded in a stereotyped fashion and were robust and flexible against a wide range of temperatures.

**Disclosures: C.R. Smarandache-Wellmann:** None. **F. Blumenthal:** None.

**Poster**

**500. CPGs: Non-Mammalian**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** DFG SM 206/3-1

UoC ZUK 81/1

**Title:** Hysteresis as source of threshold variability in neurons encoding coordinating information

**Authors: *A. C. SCHNEIDER**[1], L. SCHLAEGER[2], C. R. SMARANDACHE-WELLMANN[1]
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**Abstract:** Across the animal kingdom neural oscillators are involved in generating rhythmic neuronal activity that underlies basic functions, such as locomotion or respiration, and higher cognitive functions, such as perception and memory. Locomotion is driven by central pattern generators (CPGs) that are responsible for controlling movement of individual body segments, limbs, or joints. To produce goal-directed locomotion, the different CPGs need to be coordinated.
One model system to study the coordination of distributed CPGs is the crayfish swimmeret system which produces the same motor output *in vitro* as *in vivo*. Each of the four pairs of swimmerets on the animal's abdomen moves in alternating power-strokes (PS) and return-strokes (RS). All pairs of swimmerets move in a metachronal wave from posterior to anterior with approximately 20% phase-lag between segments. Each swimmeret is controlled by a CPG located in the corresponding abdominal hemiganglion. The four ipsilateral CPGs are coupled by the coordinating neurons $ASC_E$ and DSC. They encode information about their home module's timing, duration, and strength of PS and RS and send it to the other ganglia. The activity of $ASC_E$ is phase-locked with PS; activity of DSC is phase-locked with RS. This ensures the encoding of timing and duration. Relative burst strength is encoded by the number of coordinating spikes per burst, and the range of spikes is adapted to the average burst strength of the current motor output.
We could show in our experiments that, next to synaptic input from the CPG, the coordinating neurons possess an intrinsic hysteresis mechanism that assists in locking the activity to the motor output. For this, we recorded intracellularly from the coordinating neurons, which were chemically isolated with low $Ca^{2+}$ / high $Mg^{2+}$ saline. Stimulating the isolated neurons with repetitive triangular ramps of varying duration, amplitude, and interval, we could reveal hysteresis on two timescales. For each ramp, the first spike was elicited at a more hyperpolarized membrane potential ($V_m$) than the last spike, and more spikes were generated during the ascending than during the descending stimulus slope. This intraburst hysteresis was caused by an increase in spike threshold throughout the spiking activity. Additionally, experiments revealed interburst hysteresis on a longer timescale. In response to subsequent ramps, fewer spikes with a longer latency and at a more depolarized $V_m$ were generated. These hysteresis effects probably increase the robustness of the coordinating neurons against small fluctuations in synaptic input and allow the adaptation to the strength of the motor output by regulating their excitability.

**Disclosures: A.C. Schneider:** None. **L. Schlaeger:** None. **C.R. Smarandache-Wellmann:** None.

**Poster**

**500. CPGs: Non-Mammalian**

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**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** NIH Grant R35 NS097343

**Title:** Robustness of central pattern generating circuits to changes in pH

**Authors: *J. HALEY**, D. KUSHINSKY, D. SHIN, E. MARDER
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**Abstract:** Most neural circuits found in marine animal species must maintain function despite significant environmental changes such as temperature, dissolved oxygen concentration, and pH fluctuations in sea water. Here, we examine the effects of acute pH changes on two rhythmic motor patterns generated by the stomatogastric and cardiac ganglia of the crab, *Cancer borealis*. The pH of the haemolymph of *C. borealis* is around 7.9 while that of seawater ranges from 7.5 to 8.4 and averages 8.1. This is a 25 percent increase in acidity compared to 200 years ago, a result of ocean acidification. In these experiments, we recorded the pyloric and cardiac rhythms while varying the pH of the bath from 5.9 to 11.0. These experiments reveal animal-to-animal variability in the sensitivity of both the cardiac and stomatogastric ganglia to acute changes in pH with preparations “crashing” at varying pH values. Despite this variability, these neural circuits are extremely robust in response to external perturbations, even in extreme conditions, as preparations exhibit a normal rhythm over a 1000-fold change in proton concentration. Moreover, there appear to be fundamental differences in the pH-sensitivity of these two central pattern generating circuits that exist within the same animal with the cardiac ganglia displaying more sensitivity to basic conditions (pH > 9.5) and the stomatogastric ganglia exhibiting greater sensitivity to acidic conditions (pH < 6.5). We compare this data to the pH-sensitivity of in *vivo* cardiac and pyloric rhythms.

**Disclosures: J. Haley:** None. **D. Kushinsky:** None. **D. Shin:** None. **E. Marder:** None.

**Poster**

**500. CPGs: Non-Mammalian**

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**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** NIH Grant R35 NS097343

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**Title:** Critical slowing down as a predictor of transitions in a neuronal oscillator

**Authors: *J. M. RATLIFF**[1], T. O'LEARY[3], E. E. MARDER[2]
[2]Volen Ctr. and Biol. Dept., [1]Brandeis Univ., Waltham, MA; [3]Univ. of Cambridge, Cambridge, United Kingdom

**Abstract:** The crab Cancer borealis experiences a wide range of environments with temperatures that can vary up to 16°C in a single day as well as shifts in pH and salinity. The animal must maintain robust neural activity through all of these environmental fluctuations. The stomatogastric ganglion (STG) of the crab is able to maintain robust activity through large ranges of temperature and pH although the source of this robustness is not well understood. At more extreme temperatures and acidities, the network makes sharp transitions or bifurcations to different stable activity patterns. Recent work has proposed generic indicators to predict bifurcations under the title of "critical slowing down."
In the present study, we recorded intracellularly from the isolated pacemaker of the STG as it approaches transitions when exposed to increasing temperature (n=10) and acidity (n=10). While the temperatures and acidities at which transitions occur vary between preparations, the activity patterns that we observe are stereotyped. We also examined markers of critical slowing down, including variability and flickering, for their use in predicting transitions, and observed a marginal increase in these markers as a transition is approached.

**Disclosures:** **J.M. Ratliff:** None. **T. O'Leary:** None. **E.E. Marder:** None.

**Poster**

**500. CPGs: Non-Mammalian**

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**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** NSERC

**Title:** A developmental switch in the organization of the dedicated neural network for swimming in Zebrafish spinal cord

**Authors: *Y. ROUSSEL**, T. V. BUI
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**Abstract:** Locomotion is a fundamental task executed by the nervous system across vertebrates. However, the control of locomotion undergoes a process of maturation that occurs throughout development. This maturation process is accompanied by changes in the nervous system, both on an organizational and an operational level. Describing these changes will allow us to better understand how locomotion is controlled in mature individuals. This stereotypical motor activity can be described as a precise pattern of muscle activation operating at specific rhythms. These rhythms may arise from dedicated spinal networks named central pattern generators (CPGs). Larval zebrafish exhibit two signature rhythms: a 0.5 Hz rhythm driving the occurrence of swimming episodes and a 20 Hz rhythm driving tail beats during a swimming episode.
We focus on the 20 Hz tail beat frequency and test for the potential presence of rhythmogenic

mechanisms via application of various drugs such asstrychnine (a glycine antagonist) or heptanol (a gap junction uncoupler).
Previous studies suggest that at 3 days post fertilization (dpf), glycinergic neurotransmission is not necessary to observe 20 Hz oscillations but is needed for left-right alternation. Therefore reciprocal inhibition, a well-established mechanism for CPG operation, is not involved in rhythm generation at this developmental stage. However, heptanol was found to disturb the swimming rhythm suggesting that the electrical synapse framework is key to support swimming at that stage.
While confirming these observations at 3 dpf, our results show that strychnine completely disrupts the 20 Hz rhythm in 4 to 5 dpf fish whereas the other tested drugs had little to no effects on the rhythm. This suggests that in later developmental stages glycine plays an essential role in rhythm generation.
Furthermore, we developed a model testing the idea the possibility that maturation of swimming arises from a transition from electrical towards chemical network. The results support that even if the electrical framework is still present and required early in development, it is no more sufficient to sustained swimming in 5 dpf larvae.
Therefore, our findings support the idea of an operational shift that coincides with the transition of larval zebrafish from burst swimming to « beat-and-glide » swimming, a more mature form of swimming.

**Disclosures:** **Y. Roussel:** None. **T.V. Bui:** None.

**Poster**

**500. CPGs: Non-Mammalian**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 500.11/II22

**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** MEXT, Japan

**Title:** Critical role of En1-positive neurons for silencing slow-component neurons during fast swimming in zebrafish

**Authors: *S.-I. HIGASHIJIMA**, Y. KIMURA
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**Abstract:** Spinal neuronal circuits can produce different speeds of locomotion. It is known that some of neurons are only active during fast movements, while others are only active during slow movements. However, neuronal mechanisms how this switching is achieved are not well understood. Here, we show that V1 spinal neurons (inhibitory neurons that express En1 transcription factor) play a critical role for this in larval zebrafish. We generated transgenic

zebrafish in which En1 neurons in the spinal cord are genetically-ablated by the expression of diphtheria toxin A (DTA). These fish show defects in recruitment patterns of neurons: not only fast-component of neurons but also slow-component neurons were co-activated under the condition when wild-type fish would exhibit fast swimming. These results indicate V1 spinal neurons play a critical role for silencing slow-component neurons during fast swimming in zebrafish.

**Disclosures: S. Higashijima:** None. **Y. Kimura:** None.

**Poster**

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**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** ERC Starting Grant #311673

NIH Grant #11928047

**Title:** Combining approaches for mapping connectivity and identifying cell types in the vertebrate spinal cord

**Authors: *A. S. DUMITRESCU**, C. DELEUZE, J. ROUSSEL, M. WU, C. WYART
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**Abstract:** In the last decade the genetic identification of classes of spinal interneurons has enabled the investigation of circuits upstream of motor neurons (MNs). Of these, V2a excitatory premotor interneurons are a potential key spinal network nexus, as they span both the hindbrain and spinal cord and make direct connections onto MNs. Interestingly, recruitment of V2a neurons is speed-dependent, suggesting these interneurons could contribute to setting locomotor speed. During fast locomotion the dorsal most V2a neurons are activated, while the ventral cells are actively inhibited similar to what has been reported for motor neurons.
Currently a lot less is known about the connectivity patterns between V2a cells and MNs. Past studies tackled this question by performing challenging electrophysiological recordings from pairs of V2as and MNs, which seem to suggest a one to one mapping in terms of 'speed preference' (i.e. a 'fast' V2a – 'fast' MN etc). However, there are several possible speed-dependent network configurations within the premotor pool in terms of divergence (a single V2a neuron *can* project onto multiple motor neurons), and convergence (multiple V2a neurons *can* project onto single motor neurons). Here, we aim to increase the present V2a-MN connectivity map resolution from pairs of cells to small-scale networks (tens of cells) and eventually the full population. We will take advantage of the transparency of the zebrafish larva to implement a

comprehensive approach combining in vivo electrophysiology, state-of-the-art 3D optical stimulation of genetically targeted cells using holography and functional calcium imaging to resolve the connectivity map of V2a neurons. Our first technical challenge is to find efficient opsin actuators or inhibitors of neuronal activity in an *in vivo* zebrafish spinal cord preparation. We are currently screening the following opsins: ChR2, Chrimson, Chronos, CoChR, Halorhodopsin, ChloC, and Arch, by performing *in vivo* electrophysiological recordings of optogenetically stimulated MNs.
In parallel, we are addressing the question of V2a cell heterogeneity – which has important implications considering the potential functional differences between dorsal and ventral cells in mediating fast vs slow locomotor speeds. To this end we are performing a transcriptome analysis on V2a cell populations from larval zebrafish purified via fluorescence-activated cell sorting. Altogether these complimentary approaches should lead us to discover new ways of targeting V2a sub-populations and decipher their function and connectivity patterns in the motor pool.

**Disclosures: A.S. Dumitrescu:** None. **C. Deleuze:** None. **J. Roussel:** None. **M. Wu:** None. **C. Wyart:** None.

**Poster**

**500. CPGs: Non-Mammalian**

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**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** BMBF/NSF-CRCNS 01GQ1412 to AB, SD

**Title:** Neural mechanisms for intra- and intersegmental coupling between CPGs in an insect walking system

**Authors: C. MANTZIARIS**[1], T. BOCKEMUEHL[1], A. BORGMANN[1], S. DAUN[2], *A. BUSCHGES[1]
[1]Biocenter Cologne, Univ. of Cologne, Koeln, Germany; [2]Res. Ctr. Juelich, Inst. of Neurosci. and Med. (INM-3), 52425 Juelich, Germany

**Abstract:** In the stick insect *Carausius morosus*, segmental central pattern generating networks (CPGs) contribute to the motor output of the muscles controlling individual leg joints. Intra- and intersegmental coordination of leg stepping is mediated by both neural (i.e., sensory and central) as well as mechanical influences affecting CPGs. Information about the potential contribution of central neural influences to the intersegmental interaction between segmental CPGs still remains elusive (Borgmann and Bueschges, 2015, COIN).
Here, we investigated central interactions between ipsi- and contralateral segmental CPGs that control motor output of the muscles that move the coxa-trochanter (CTr) leg joint. We recorded

the activity of motor neurons (MNs) innervating the depressor trochanteris muscles in all three isolated or interconnected thoracic ganglia. Rhythmic activity in leg MN pools was induced by application of the muscarinic acetylcholine receptor agonist pilocarpine (Bueschges et al. 1995, J Exp Biol). Potential CPG coupling interactions were determined using either phase analysis of the evoked rhythmicity or correlation of contralateral depressor spike activity.
Our results reveal weak intrasegmental coupling between hemisegmental CTr-CPGs. Contralateral CPGs exhibit specific and variable phase relationships in each isolated thoracic ganglion (i.e., anti-phase in the meta-, in-phase in the meso- and no coupling in the prothoracic ganglion). However, in interconnected ganglia, CPGs show a clear tendency for inter- and intrasegmental in-phase activity. Currently, we are studying the network mechanisms that contribute to CPG coupling. For this, we analyze premotor interneuron and MN activity in hemisegmental CPGs by means of intracellular recordings after lesioning commissural tracts between hemisegments.

**Disclosures: C. Mantziaris:** None. **T. Bockemuehl:** None. **A. Borgmann:** None. **S. Daun:** None. **A. Buschges:** None.

**Poster**

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**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** R00-DC012536

Pew Biomedical Scholars

Alfred P. Sloan Foundation

**Title:** Heterogeneity of V2b premotor neurons in zebrafish spinal cord

**Authors: *R. CALLAHAN**[1], Y. KIMURA[2], S.-I. HIGASHIJIMA[3], M. BAGNALL[1]
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**Abstract:** Precise body movements necessitate the coordination of diverse motor pools, which are governed by premotor circuits consisting of different classes of excitatory and inhibitory spinal cord interneurons. The V2b (GATA3+) premotor population, which provides ipsilateral inhibition to motor neurons, has been implicated in regulating flexor-extensor alternation in mouse, positioning it as a key component in the coordination of motor pools (Britz et al. 2015; Zhang et al. 2014). However, to date no study has comprehensively described the anatomy, physiology, connectivity, or functional activity of V2b neurons. We have leveraged the genetic

tractability, transparent skin, and spinal cord accessibility in zebrafish larvae to study the basic anatomy and diversity of V2b neurons identified in GATA3:Lox-RFP-Lox:GFP or GATA3:Gal4; UAS:GFP transgenic animals. All V2b neurons project their axons exclusively ipsilaterally and caudally, though with few ascending collaterals, in contrast with the V2a population (Menelaou et al. 2014). Axon projections exhibit heterogeneity in their dorsoventral trajectories. In contrast with mouse, where the majority of V2b neurons co-express GABAergic and glycinergic markers, the V2b population in zebrafish expresses the glycinergic marker GlyT2 in cell bodies located in the dorsal portion of the cord, whereas the GABAergic marker Gad1b is expressed in more ventrally located V2b neurons. We employed functional imaging to monitor the activity of V2b neurons during locomotion, pairing light sheet microscope imaging of calcium transients in GATA3:Gal4; UAS:GCaMP6f animals with ventral root physiology. Our findings reveal that while general recruitment of V2b neurons is coincident with a swim event, the timing of calcium peaks in relation to the swim bout varies. The anatomical and functional diversity observed in the V2b population suggests the presence of multiple distinct subpopulations, in keeping with recent lines of evidence that each genetically defined spinal population comprises discrete subpopulations (e.g., Menelaou et al 2014; Bikoff et al. 2016; Dyck et al. 2012). Overall these data indicate a more complex vertebrate premotor circuitry than has been previously appreciated.

**Disclosures:** **R. Callahan:** None. **Y. Kimura:** None. **S. Higashijima:** None. **M. Bagnall:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.01/II26

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Chinese government

**Title:** Establishment of a theory on target neural regeneration guided by dorsal root stumps for repairing complete spinal cord transection in adult animals

**Authors: *S. LIN**, T. ZHAO, T. TANG, J. GAO, S. YANG, X. ZHANG, F. KONG, X. LIN, Z. YONG, J. MA, X. WENG, S. JING, S. LIU
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**Abstract:** It is well known that dorsal root nerve fibers enter the posterior horn of spinal cord and innervate interneurons of central pattern generation in grey matter. If intercostal nerves or graft nerves delivering signals from supraspinal structures are anatomized to the proximal stumps of dorsal root, the residual myelin or neurolemma of nerve fibers in dorsal root might guide the

regenerating nerve fibers to grow into lower spinal cord, and form synapses with the interneurons that the dorsal root nerve originally innervate. Thus, a novel hypothesis that target neural regeneration guided by proximal stump of dorsal root nerve for repairing spinal cord injury was put forwarded based on the neural anatomy, the neuropathology and the motor neural circuits.
To verify the hypothesis, TRDA and FDA were microinjected either into L4 dorsal root and corticospinal tract, or rubrospinal tract and L4 dorsal root, or into L3 and L4 dorsal roots. Varicosities of different origins were observed to co-contact with various neurons in the gray matter of L3-L4 segments of spinal cord. Furthermore, six months after T11 intercostal nerve-L3 dorsal root anastomosis, TRDA and FDA were microinjected into the T11 intercostal nerve and L4 dorsal root, and the same triple labeled images in L3- L4 cord levels have been detected. The results showed that T11 intercostal nerve-L3 dorsal root anastomosis could reconstruct the connections of the upper and the lower spinal cords.
T11 intercostal nerves-L3 dorsal root stumps anastomosis were performed immediately or lingeringly for repairing lower thoracic spinal cord complete transection in rats, and the anastomosis sites were treated with neurotrophin/growth
factor cocktail. Following the surgery, partial hind limb locomotion recovered gradually. Six months after target repairing, mean BBB scale of hind limb was 14.75±2.10. Regenerative fibers from T11 intercostal nerves were traced to grow into L3 dorsal root stumps and posterior horn, eventually contact with neurons in the gray matter of the spinal cords between L2 and L4. Electrostimulation of the bridged nerves could trigger evoked potentials in sciatic nerve, bladder and colon, and cause locomotion of hind limbs. When the bridged nerves were transected, the evoked potentials and hind limbs locomotion disappeared. Two months after intercostal nerve-lumber dorsal root anastomosis, the hind limbs of the adult monkeys accepted spinal cord complete transection could also move autonomously.
The evidences indicate that the theory on target neural regeneration guided by dorsal nerve root is potentially applicable for repairing the complete functional loss of spinal cord injury in clinical practice.

**Disclosures:** **S. Lin:** None. **T. Zhao:** None. **T. Tang:** None. **J. Gao:** None. **S. Yang:** None. **X. Zhang:** None. **F. Kong:** None. **X. Lin:** None. **Z. Yong:** None. **J. Ma:** None. **X. Weng:** None. **S. Jing:** None. **S. Liu:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.02/II27

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Department of Veterans Affairs VA Merit Review B78071/1I01RX000502-01A and Award No. 0612BRRC-7, BRRC Pilot Initiative

**Title:** Electro-acupuncture and pregabalin alleviated spasticity and orofacial and somatic allodynias in a clinically relevant rodent model of closed head traumatic brain injury

**Authors: *P. K. BOSE**[1,2,3], J. HOU[1,2], G. MUSTAFA[1,2], R. NELSON[1], J. WATTS[1], S. TSUDA[1,2], J. GODWIN[1], H. P. RAMIREZ[4], F. J. THOMPSON[1,2,5]
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**Abstract:** TBI-induced spasticity and chronic pain/headache are major health issues in both military and civilian personnel. The objective of this current work is to test the effectiveness of two individual treatments, Electro-acupuncture (EA) and pregabalin (Lyrica) in TBI-induced spasticity and pain-like behaviors in a clinically relevant rodent model of closed head traumatic brain injury (cTBI). In this model we have shown comprehensive evidence of progressive and enduring spasticity (Bose et al., 2013; Hou et al., 2017), and orofacial and somatic allodynia, a hypersensitive pain response induced by non-painful stimulation (Mustafa et al., 2016, 2017). Pregabalin (225ul orally, twice daily for 4 weeks), and EA stimulations were applied immediately after TBI in two separate cohorts of TBI animals as preemptive acute treatments. Six 30 minute sessions of EA stimulation were performed over 2 weeks at 6 acupuncture points using continuous 10 Hz stimulation at an intensity of 3 mA. The velocity-dependent ankle torques, time-locked triceps surae EMGs, H-Reflex testing, and a reward-conflict operant testing paradigm were applied to test spasticity and orofacial allodynia, respectively. In the later paradigm, the rat may choose to access a sweetened milk reward through facial contact with a mildly nociceptive thermal stimulation. The Orofacial Pain Assessment Device (Stoelting, Co) provides a peltier contact window whose temperature can be heated to mildly aversive temperatures. We used a standard hot plate peltier device to test plantar paw lick latencies at 37 - 46 deg C. The cTBI animals showed significant decreases in reward and also plantar lick latency to thermal heat test stimuli, hallmark behaviors for facial and somatic allodynias. Our data to date indicate that animals receiving either treatment exhibited a significant reduction in orofacial and somatic allodynia. In addition, animal receiving either treatment showed significant improvement in physiological indices of spasticity compared to untreated injured control animals. Studies in progress are assessing therapy-induced changes in a comprehensive array of biomarkers, molecules, and receptors related to spasticity and pain signaling and inflammation in the trigeminal and somatic pain pathways. Progressively, these studies may increase our understanding of the neurobiology of TBI-induced spasticity and pain, and the potential mechanisms of action of experimental therapies utilizing EA and pregabalin. The goal of these studies is to enhance the opportunity for the translation of safe and effective treatments for human TBI injury-induced spasticity and pain/headache conditions.

**Disclosures: P.K. Bose:** None. **J. Hou:** None. **G. Mustafa:** None. **R. Nelson:** None. **J. Watts:** None. **S. Tsuda:** None. **J. Godwin:** None. **H.P. Ramirez:** None. **F.J. Thompson:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.03/JJ1

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Medtronic, PLC.

VA Merit Review B6570R

**Title:** Intrathecal baclofen (ITB) combined with locomotor exercise provides better therapeutic outcome in reducing spasticity, improving anxiety, cognitive and activity performance, and no adverse effect on balance performance in a traumatic brain injury (TBI) rodent model

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**Abstract:** Spasticity is a major health problem for patients with moderate to severe TBI. Progressively developing spasticity following TBI often represent one of the most significant barriers for practical re-entry of TBI patients into the community. The objective of this preclinical study was to evaluate the safety and efficacy of acute ITB treatments and treadmill locomotor training (Tm), individually and as combined therapy. We employed a comprehensive series of long-term quantitative outcome measures to compare new versus standard of care with ITB treatment following TBI, where this combination therapy appears to potentially represent a paradigm shift in rehabilitation therapy. In these studies ITB (Lioresal® baclofen injection; 0.8µg/hr) and Tm were initiated at one week after injury in a clinically relevant rodent TBI model where we observed enduring spasticity, balance, anxiety and cognitive deficits (Bose et al. 2013; Hou et al. 2017) (Marmarou model; 450g/1.5 m). Spasticity, anxiety-like behavior, balance, cognitive, and home cage activity performances were measured using velocity-dependent ankle torque, an elevated plus maze (EPM), rotorod, Morris water maze (MWM), and Noldus Phenotyper, respectively. One month of ITB and Tm combined treatment completely blocked early onset spasticity and also positive impacts on cognitive, balance, anxiety and activity recoveries. More importantly, this significant therapeutic benefit persisted even after cessation of ITB therapy. The combined therapy group exhibited significantly reduced MWM latency at the fourth day of testing, and significantly less anxiety-like behavior in the EPM. Twelve hour video-tracked activity monitoring data (recorded 6pm - 6am) revealed that compared with non-treated TBI animals, the ITB+Tm group exhibited home caged behavioral

patterns that were most similar to normal animals. These observations indicated that initiating ITB in combination with a Tm produced a robust rehabilitation that was more effective than either therapy implemented individually. This improved spasticity outcome was accompanied by marked up-regulation of GABA/$GABA_b$, norepinephrine and BDNF expression in the spinal cord tissue. These data will be compared and discussed with a data set derived from another study where ITB treatment alone initiated at a chronic time point (post-TBI 1 month) showed less attenuation of spasticity, and it adversely affected balance performance. These broad spectrum of comprehensive data may reinforce confidence in the safety, feasibility, and efficacy of early intervention ITB treatments for TBI using with locomotor and ITB therapy for TBI-spasticity.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.04/JJ2

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** the United States (U.S.) Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D) Merit Review Award # B1005-R/1I01RX001005-01A2

**Title:** Simultaneous application of treadmill locomotor exercise and magnetic stimulation improved cervical spinal cord injury (C-SCI)-induced spasticity and gait disabilities in acute and chronic setting

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**Abstract:** Cervical spinal cord injury (C-SCI) is a common and frequently devastating injury that can result in a broad range of life-long locomotor impairments, including spasticity and gait disabilities. We recently reported that a serial combination of treadmill locomotor exercise (Tm) with SCI-site magnetic stimulation yielded significant improvement in spasticity and gait (Hou et al., 2014). In order to potentially improve the efficacy of the therapy, here, we evaluated the therapeutic effects of simultaneous application of Tm with injury-site magnetic stimulation

initiated at post-injury (pi) acute and chronic time points. Moderate $C_{6/7}$ contusion injuries (200 kdynes, Infinity Horizon Impactor) were produced in 30 anesthetized adult Sprague-Dawley rats (randomly selected; acute group, n=20; chronic group, n=10). In the acute group, Tm was initiated at pi-day 8, for 5 days each week. Beginning at pi day-14, magnetic stimulation was applied at the injury site simultaneously with Tm, every other day, for 6 weeks. We used a single pulse protocol that we have recently reported (Hou et al., 2014). For the chronic simultaneous treatment group, five rats initiated Tm and magnetic stimulation at pi week-8 and continued for six weeks using the above mentioned treatment regimen. As a measure of spasticity, velocity-dependent ankle torques, and time-locked triceps surae EMGs were recorded at pi week-4 and week-8 for the acute group, and at pi week-8 and week-14 for the chronic group. In the acute group, six weeks of treatments completely blocked the development of spasticity when compared to data obtained from untreated injured controls. However, spasticity was significantly reduced but not completely blocked in the chronic treatment group. To potentially probe mechanisms associated with the therapeutic benefits, to date we have performed immunohistochemistry of the lumbar spinal tissue for the acute group. These results showed robust treatment-induced up-regulation of dopamine beta-hydroxylase, gamma-aminobutyric acid receptor and glutamate decarboxylase. To date, our data suggest that simultaneous application of Tm locomotor exercise and magnetic stimulation at the cervical injury site can be an effective treatment for C-SCI induced spasticity, with acute treatment showing greater efficacy than the chronic treatment. Potential mechanisms of the therapeutic benefits point towards enhancing the descending modulation of presynaptic and postsynaptic factors (noradrenergic and the GABAergic) that regulate motoneuron excitability.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.05/JJ3

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** NIH Grant R01-NS079751

**Title:** Effects of locomotor training intensity on sympathetic-somatomotor coupling in spinal cord injury

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**Abstract:** In people with spinal cord injury (SCI), impaired connectivity between supraspinal and spinal segments below the injury impairs the sympathetic and somatomotor nervous system below the level of the injury. Proper coupling between the systems allows normal physiologic responses during exercise, in which sympathetic and somatomotor systems work together to regulate cardiovascular responses. However, after SCI, improper sympathetic-somatomotor coupling can have deleterious effects during exercise and limit rehabilitation outcomes. The purpose of this study was to understand how locomotor treadmill training affects sympathetic-somatomotor coupling in people with incomplete SCI. Thirteen people (49.8 ± 7.2 years) with motor incomplete spinal cord injuries (ASIA C or D; injury level > T6) participated in a locomotor treadmill training program. Patients were randomized into either a high-intensity (HT; 70-85% of maximum predicted heart rate) group or a low-intensity (LT; 50-65% of maximum predicted heart rate) group, and completed locomotor training over 4-6 weeks, 3-5 days/week. Prior to and following training, we tested sympathetic-somatomotor coupling by eliciting reflexive sympathetic activity via a cold stimulation, noxious stimulation and a mental math task while we measured tendon reflexes, blood pressure and heart rate. We found that patients with incomplete spinal injuries who completed the high-intensity locomotor training protocol exhibited reduced stretch reflex excitability during elevated sympathetic activity. We also observed a trend of increased mean arterial pressure in the HT group compared to the LT group. These results suggest that high-intensity locomotor training may be advantageous to low-intensity training to improve sympathetic-somatomotor coupling in people with incomplete SCI.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.06/JJ4

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** USAMRAH #SC140038

**Title:** Epidural stimulation and pharmacological blockade of fast inhibition improve respiratory pacing following complete spinal cord injury

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**Abstract:** The use of epidural stimulation (ES) in patients with spinal cord injury (SCI) has gained increased media attention in the past decade with significant success demonstrated in human studies, including improvement of lower limb motor function in paraplegic patients.

DiMarco, Kowalski and colleagues were first to investigate ES applied to T1-T2 ventral surfaces to restore respiratory function following high cervical spinal cord transection. In the current study we combine ES (at C3-C5 segments corresponding to area of phrenic motor pool) and pharmacological strategies (blocking of GABAa and Glycine inhibitory receptors) for more specific activation of spinal interneurons and motoneurons involved in the shaping of respiratory motor output following C1 transection (C1Tx). All experiments were performed in decerebrate, unanesthetized adult Sprague-Dawley rats, 5-6 h post C1Tx. ES was applied to ventrolateral surface of C3-C5 cervical segments bilaterally via teflon-coated silver (0.01'' bare and 0.013'' coated, AM-Systems) stimulating electrodes (0.2 ms biphasic stimulation, 100-200 Hz during 0.3 s, one train per sec). Prior to pacing procedure, the minimal thresholds (Tr) of current (87.4±10.3 for C3, 73.6±8.2 for C4 and 84.7±8.2 mkA for C5 segments) affecting tracheal flow and end-tidal CO2 level were detected. ES applied to the C4 level (~ 5 Tr, 350.7±41.2 mkA) produced non-fatigue contraction of chest and diaphragm muscles with stable tracheal flow (2.3±0.21 ml of tidal volume) and end-tidal CO2 (4.5±0.3 %) during 1 h. In contrast, ES applied to C3 or C5 segments required much higher current (~ 7 Tr, 633.8±84.5 mkA) with development of muscle fatigue in 5 out of 8 rats. Ten minutes after intrathecal administration of 30 mkl (25 mkMol) of GABAzine and strychnine (blockers of GABAa and glycine inhibitory receptors, respectively) the minimal thresholds were significantly decreased for all segments (62±7.9 for C3, 41.1±6.4 for C4 and 67.9±7.3 mkA for C5). The tidal volume was increased by 43% (3.3±0.27 ml) during C4 pacing and fatigue of respiratory muscles was observed in 2 out of 8 rats during ES of C3 or C4 segments. Based on our results, we conclude that spinal respiratory circuits are tonically inhibited after C1Tx and their pharmacological modulation has the potential to improve ES in patients with SCI.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.07/JJ5

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Craig Neilsen Foundation Grant # 338237

**Title:** Development of a novel automated device for the assessment and training of skilled locomotion in spinal cord injured rats

**Authors: *T. RICHARDS**[1], P. SHARMA[2], A. KUANG[3], P. K. SHAH[1,2]
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**Abstract:** Although cervical spinal cord injuries (cSCI) account for more than 62% of all SCIs, much less is known about the skilled locomotor recovery of the forelimb and hindlimb following a cSCI. Skilled locomotion is commonly assessed using the horizontal ladder task. However, the non-uniform speed of rats on the horizontal ladder introduces a great source of variability in speed and completion time of the task. Moreover, fine impairments in motor function are compensated by variable walking speeds across the ladder as most rats are unable to complete the task uninterrupted, especially after CNS damage. To overcome limitations posed by the horizontal ladder, in the present work, we have developed a novel Automated Device for the Assessment and Training of Skilled locomotion (ADATS) for adult rats. ADATS is a custom-built device consisting of two circular shaped Plexiglas walls joined together by metal rungs unevenly spaced around the edges. Powered by an integrated step motor, the ADATS rotates in the clockwise or anticlockwise directions at a predetermined tester defined speed, thereby forcing the rats to step at a constant speed. Our rationale is that since motor compensation by speed is eliminated, motor impairments, if any, can be easily discerned. ADATS is also equipped with cables that can facilitate the recording of EMG data to visually display the functional state of the spinal cord. Herein, we validate ADATS as a tool for assessing functional motor recovery of the forelimbs and hindlimbs in ten adult rats subjected to a cervical dorsal crush injury at C4. Skilled locomotor behavior was assessed both on the ADATS as well as on the horizontal ladder using a standard 7-point skilled locomotor scale at multiple time points for ten weeks. We used high resolution video (60 fps) for frame by frame qualitative and quantitative analysis of step placement on the rungs. Our findings demonstrate that there is wide speed variability between and within trials when rats are tested on the horizontal ladder. In contrast, rats tested on ADATS display uniform walking speeds on ADATS as predetermined by the tester. Furthermore, after a cSCI, limb placement errors on ADATS are highly comparable with that of the horizontal ladder at lower speeds. Additionally, at higher speeds on ADATS, the extent of limb placement errors significantly increases. Importantly, ADATS also reveals gross and subtle motor deficits that are undetected by the horizontal ladder. These data are unique and validate the use of ADATS as a sensitive skilled locomotor assessment tool for pre-clinical experimentation.

**Disclosures:** **T. Richards:** None. **P. Sharma:** None. **A. Kuang:** None. **P.K. Shah:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.08/JJ6

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Craig Neilsen Foundation Grant # 338237

**Title:** ADATS (automated device for the assessment and training of skilled locomotion) in action: Assessment and training of inter-limb coordination after a cervical spinal cord injury in rodents

**Authors: *P. D. SHARMA**[1], T. RICHARDS[2], A. KUANG[3], P. SHAH[1,2]
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**Abstract:** The horizontal ladder has been used for decades to assess the skilled locomotor recovery following a spinal cord injury (SCI). One aspect that poses a threat to the validity of findings in which the horizontal ladder is used is the lack of speed control during task performance. Differences in walking speeds in rats between experimental trials result in different profiles of coordination. Rats with slower speeds can mask the true coordination deficits as they get more time to compensate for their motor deficits, and many of the subtle coordination deficits go unnoticed. This makes the quantitative interpretation of forelimb-hindlimb (FL-HL) recovery and inter-limb coordination (ILC) difficult. One potential approach of overcoming this confounding factor is to develop an assessment device that controls for the pace at which the rats walk during skilled locomotion. A novel device, ADATS (Automated Device for the Assessment and Training of Skilled locomotion) developed in our laboratory, adds varying degrees of complexities to skilled walking due to its speed control mechanism and ensures uniform speed during locomotion. The main objective of this study is to validate the use of ADATS in assessing ILC coordination following a SCI, and to explore the capacity of ADATS as a motor rehabilitative training tool. Adult rats received a dorsal crush injury at C4. ILC was assessed using seven end points of limb coordination. Training capabilities of ADATS were investigated using stepping patterns and limb engagement during task execution. Our preliminary data show that ADATS is able to capture coordination deficits in all seven end points of ILC to a greater extent than the horizontal ladder. Also, with the use of ADAPTS, rats exhibit an increased proportion of quadrupedal stepping pattern and engagement of forelimbs during skilled locomotion. Our findings also reveal, for the first time, that skilled locomotor deficits are chronically persistent even after mild cervical SCIs. Collectively, these findings suggest that use of currently available tools such as the horizontal ladder alone may not be sufficient if fine motor skills or subtle effects of interventions are to be assessed accurately after SCIs. The sensitivity, accuracy, and consistency with which data are obtained using ADATS provides a strong rationale for using it as a standardized assessment system to assess ILC deficits after a SCI. In addition, ADATS can also function as a forced therapeutic tool because rats are compelled to engage their forelimbs and hindlimbs during walking to keep up with the demanding speeds of ADATS.

**Disclosures: P.D. Sharma:** None. **T. Richards:** None. **A. Kuang:** None. **P. Shah:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.09/JJ7

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Craig Neilsen Foundation Grant # 338237

**Title:** Consistencies and disparities in supraspinal and spinal neuronal mechanisms dictate the extent of commonalities in forelimb locomotion behaviors

**Authors: *M. ISLAM**[1], T. PENG[1], P. SHAH[2]
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**Abstract:** Treadmill and ladder walking tasks have been used routinely to assess functional motor recovery after neurological dysfunction in rodents. Our preliminary data presented earlier showed that common neuronal drive regulates rhythmic treadmill (TM), overground (OG) and ladder (LAD) walking behaviors in awake adult rats. In this work we expand on those findings and ask to what extent OG, TM, and LAD walking tasks share commonalities of neuronal input. Specifically, our aims are: i) to determine commonalities in EMG activation patterns, motor unit (MU) recruitment and firing rate of treadmill slow (TMS: 13cm/s), fast (TMF: 21cm/s), LAD and OG walking tasks ii) to determine commonalities of neural input in TM and LAD walking tasks in relationship to OG walking. 8 adult rats were implanted with EMG electrodes in 4 muscles: deltoid (DEL), bicep (BB), flexor digitorum superficialis (FDS), and extensor digitorum (ED). Raw EMG bursts of each muscle (> 50 bursts) were filtered, rectified, and normalized to step cycle durations to obtain EMG activation patterns. Also, a 2s processed-EMG signal from each forelimb muscle for each task was extracted to quantify the mean rectified value (MRV: the extent of MU recruitment) and mean power frequency (MPF: rate of MU firing) for categorical cluster analysis. These EMG segments were also used for coherence analysis to determine sources of common neural input between tasks. Our results demonstrate that EMG activation patterns are similar for both proximal (DEL and BB) and distal (FDS and ED) muscles between tasks, except for LAD where FDS muscle has distinct timing of activity. Cluster analysis grouped MRV into 2 clusters: C1 and C2, consisting of OG, TMS, and TMF, and LAD walking, reflecting commonality in recruitment of MU between tasks, except for the LAD. MPF features were grouped into 3 clusters: C1 for OG and TMS, C2 for TMF, and C3 for LAD walking. MPF clusters demonstrated a sizable overlap that suggests commonality in firing of MU between three tasks. Coherence analysis showed significant peaks in almost all cases suggesting the presence of common neural input (supraspinal & spinal) between tasks. The number of these significant peaks were 3-8 in the entire frequency range (1-100 Hz), which suggests diverse sources of neural input between behaviors. Notably, the dominant frequency at

which peak coherence occurs ranged from 11.6-29 Hz across the tasks and muscles used, which indicated that these tasks are dominated by various cortical structures including motor cortical inputs that range from 10-30 Hz. Our results are novel and suggest the presence of common spinal and supraspinal inputs in the rhythmic forelimb locomotor tasks in adult rats.

**Disclosures:** **M. Islam:** None. **T. Peng:** None. **P. Shah:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.10/JJ8

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** ARO W911NF1410141 - 64929EG

**Title:** Selective excitation of large diameter sensory afferents with DREADDs enhances functional recovery post-spinal cord injury

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**Abstract:** *Motivation*: It has been demonstrated that sub-threshold epidural stimulation of the lumbar spine can allow voluntary body-weight support, stepping, and leg movement in cases of chronic spinal cord injury (SCI). These studies used electrical stimulation thought to only excite large diameter sensory afferent (LDSA) neurons, but may have had off-target effects (e.g. excitation of pain pathways, known to inhibit motor learning). We sought to develop an alternative approach to excitation of LDSA using designer receptors exclusively activated by designer drugs (DREADDs). DREADDs facilitate genetically targeted neuromodulation, and do not require implantation of stimulating hardware or tethering. They also allow mapping of cells affected by DREADDs and their second order connections.
*Background:* DREADDs are a modified human muscarinic receptors that respond to the drug clozapine-N oxide (CNO) and that can excite or inhibit neurons via G-protein pathways on the hour time-scale. We have previously modulated H-reflex excitability using virally expressed DREADDs in intact rats, and here extend this approach for SCI rehabilitation. We hypothesized that use of DREADDs throughout SCI recovery would result in fewer incidences of foot drag and a more extended limb posture post-SCI during over-ground gait.
*Methods:* One month prior to SCI, five female Sprague-Dawley rats were exposed to a viral vector designed to express the excitatory DREADD hM3Dq (AAV2-hSyn-hM3Dq-mCherry). DREADDs were confined to LDSA of dorsal root ganglia (DRG) L2-L4 through a combination of surgical (direct DRG injection) and viral (2-4µl of AAV2 at 5 X $10^{12}$ MOI) approaches. Two

weeks after viral infusion, animals were trained to walk on a treadmill in 5 minute bouts at 5 fixed speeds (16-32 cm/s in 4cm/s increments) interleaved with a 1 minute rest period. This was done three times a week for 2 weeks, after which we performed a T9-T10 hemisection. Following a one week recovery period, animals received 6 additional weeks of training at the same speeds and duration used pre-SCI, with CNO administration (2mg/kg) 30 minutes prior to the start of training. SCI control subjects (n=5) received the same treadmill training pre-SCI and post-SCI without virus exposure or CNO administration. We collected kinematic data pre-SCI, during initial training post-SCI, and every two weeks post-SCI at all 5 speeds.
*Results:* Preliminary analysis of these data show a significant reduction in rate of foot-drags by 48% for DREADDs animals compared to SCI controls, at six weeks post injury, at a walking speed of 20 cm/s (linear mixed effects model; p=0.043, n=5 rats). Further analysis of kinematic and foot drag data is ongoing.

**Disclosures: B.D. Robertson:** None. **G.M. Smith:** None. **M.A. Lemay:** None. **A. Spence:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.11/JJ9

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** CRSNG Grant 05403

**Title:** Inflammatory nociception attenuates training induced locomotor recovery after spinal cord injury by altering KCC2 expression

**Authors: *R. JEFFREY-GAUTHIER**[1], M.-P. COTE[2], M. PICHE[3], H. LEBLOND[4]
[1]Univ. Du Québec À Trois-Rivières, Trois-Rivières, QC, Canada; [2]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [3]Dept. de Chiropratique, Univ. Du Quebec A Trois-Rivieres, Trois-Rivieres, QC, Canada; [4]Anatomie, Univ. du Quebec a Trois-Rivieres, Trois-Rivieres, QC, Canada

**Abstract:** Following spinal cord injury (SCI), neuroplasticity in spinal network contributes to motor recovery but also to hyperreflexia, spasticity and neuropathic pain development. Activity-dependent therapies such as locomotor training foster functional recovery. However, its extent can be critically limited by the presence of acute and chronic pain. It was recently shown that training positively influences recovery by increasing the expression of the chloride cotransporter KCC2 in lumbar motoneurons suggesting a restoration of inhibitory GABAergic and glycinergic transmission. In complete SCI mice, we showed that inflammatory nociception from complete Freund adjuvant (CFA) injection in sublesional back muscles attenuates training's positive

impact on locomotion without affecting the H-reflex frequency-dependent depression (FDD) recovery. The purpose of this study was to evaluate if CFA injection decreases locomotor recovery by preventing the activity-dependent increase in KCC2 levels associated with training. Four groups of CD1 female mice composed of control spinal mice (n=8), trained spinal mice (n=7), spinal mice with CFA (n=7) and trained spinal mice with CFA (n=6) were completely transected at T7. Hindlimb treadmill locomotion was assessed prior to SCI and on day 7, 14, 21 and 28 post-SCI. In a terminal experiment, the animals were decerebrated and H-reflex, elicited by tibial nerve stimulation, was evaluated at different frequencies (0.2, 5, 10, 0.2 Hz) to assess the FDD. The spinal cord were harvested and lumbar levels of KCC2 measured by Western blotting and compared with immunohistochemistry visualization of KCC2 staining in lumbar spinal cord sections. Additionally, phospho-p38 expression was measured as a marker of neuroinflammation associated with CFA injection. Our results show that CFA injections prevented the restoration of KCC2 expression levels in the lumbar spinal cord. Decreased KCC2 expression was associated with decreased knee angular excursion, increased paw drag and impaired H-reflex depression at 5 Hz and 10 Hz compared to baseline. Similarly, increased levels of phospho-p38 was associated with decreased knee angular excursion, increased paw drag and decreased reflex depression at 5 Hz and 10 Hz. This study suggests a potentially relevant mechanism on the interplay between training and inflammatory nociception and his highly relevant to most SCI individuals that present concurrent musculoskeletal tissue damage.

**Disclosures: R. Jeffrey-Gauthier:** None. **M. Cote:** None. **M. Piche:** None. **H. Leblond:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.12/JJ10

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** NIH Grant NS083666

CHNF 316299

**Title:** Enhancing chloride extrusion restores reflex modulation after spinal cord injury

**Authors: *J. BILCHAK STROUGHAIR**, M.-P. COTE
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**Abstract:** Over 75% of spinal cord injured (SCI) individuals experience spasticity with incapacitating symptoms ranging from increased muscle tone to involuntary movements and hyperactive reflexes. We have previously reported that hyperreflexia is attenuated by exercise after SCI through an increase in KCC2 expression in lumbar motoneurons (Côté et al., 2014).

The expression of the chloride cotransporters KCC2 (extruder) and NKCC1 (intruder) largely determine the intracellular concentration of chloride ($[Cl^-]_i$) which in turn significantly affect postsynaptic inhibition through $GABA_A$ and glycine receptors. Consequently, a disruption in chloride homeostasis contributes to several neurological disorders including hyperalgesia, chronic pain, epilepsy and motor spasticity.

Although exercise has the potential to restore chloride homeostasis after SCI, early post-injury implementation of a rehabilitation programs in the clinic is often problematic. Here, we sought to determine if pharmacologically increasing KCC2 expression/activity improves reflex recovery after SCI. We also assess if it has the potential to further enhance activity-dependent recovery. Restoring chloride homeostasis will be achieved using CLP257, a chloride extrusion enhancer, which rescues KCC2 plasma membrane expression and has been shown to successfully alleviate hypersensitivity in models of neuropathic pain (Gagnon et al., 2013).

Adult female Sprague Dawley rats underwent a complete transection (T12) and were assigned to one of 3 groups: 1) untrained, 2) bike-trained or 3) step-trained. During a terminal experiment (4-8 weeks post-SCI), H-reflexes were evoked by the stimulation of the tibial nerve and recorded in the interosseous muscles. Hyperreflexia was estimated by measuring the frequency-dependent depression of the H-reflex (FDD) before and after CLP257 (100uM) was directly applied to the lumbar enlargement of the spinal cord. Spasticity was also assessed using quick stretches of the triceps surae using a dual-mode muscle lever. Our results indicate that CLP257 restores FDD in untrained animals but did not affect trained animals that had already recovered FDD through a rehabilitation program. As expected, the normalization of the FDD response was associated with a decreased $H_{max}/M_{max}$ ratio. Surprisingly, although CLP257 was without effect on the FDD, it significantly increased $H_{max}/M_{max}$ ratio, especially in step-trained animals. Our results suggest that pharmacologically targeting KCC2 activity has the potential to improve reflex recovery after SCI.

**Disclosures:** **J. Bilchak Stroughair:** None. **M. Cote:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.13/JJ11

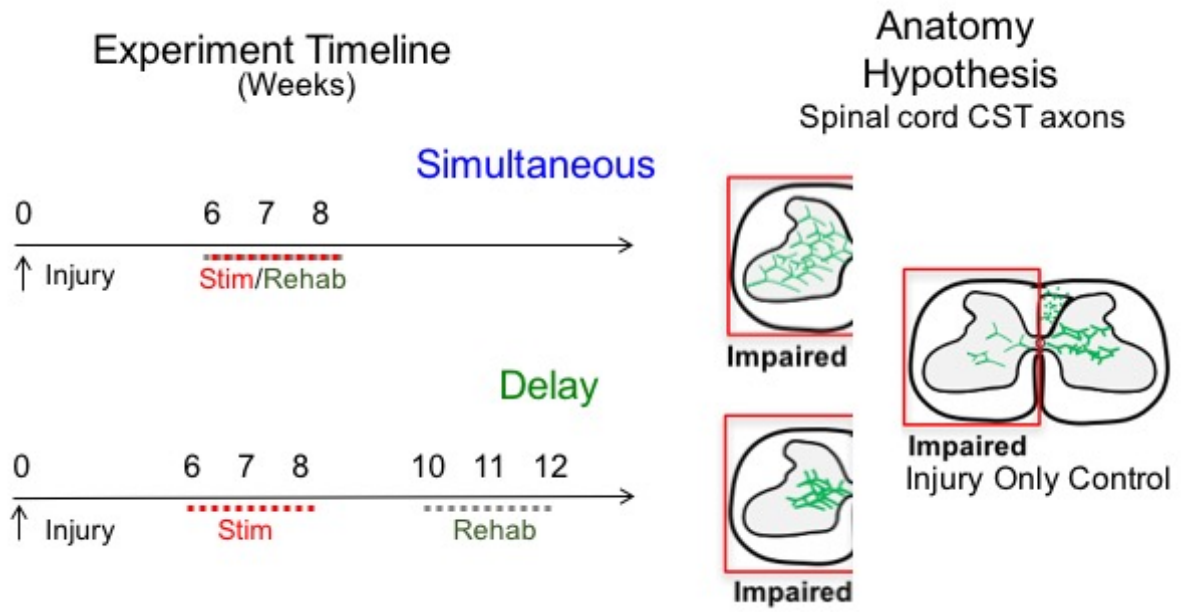
**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** New York State Department of Health (NYSDOH) Spinal Cord Injury Research Board (SCIRB) DOH01-C30598GG-3450000

**Title:** How timing of rehabilitation after electrical stimulation on rats with chronic corticospinal tract injury effects augmentation of functional recovery

**Authors: *T. T. BETHEA**, J. SANTOS, H. PARK, A. SINDHURAKAR, J. CARMEL
Burke-Cornell Med. Res. Inst., White Plains, NY

**Abstract:** Rehabilitation is standard care after injury to the brain and spinal cord. As we look to incorporate therapies that promote nervous system repair into clinical practice, there is a gap in our understanding of how and when to combine restorative therapies into rehabilitation. Our laboratory has previously shown that electrical stimulation applied to the uninjured corticospinal tract after partial injury improves functional recovery and promotes axonal outgrowth in rats. The goal of our study is to determine the proper timing between electrical stimulation and rehabilitation. We hypothesize that electrical stimulation delivered two weeks before rehabilitation will be more effective than simultaneous application of the two therapies. Adult Sprague-Dawley female rats received a cut lesion of one corticospinal tract (pyramidotomy). Six weeks later, electrodes were implanted over motor cortex, and used to deliver 10 days of electrical stimulation, 6 hours a day, using our previously published protocol. Rats were randomized to receive rehabilitation during the stimulation period (30 minutes after stimulation) or 2 weeks later. To quantify forelimb skill, we used the knob task that measures supination, a critical component of forelimb dexterity that is impaired after corticospinal injury in both rats and humans. To quantify changes in corticospinal axon density, we anterogradely traced axons with biotinylated dextran amine and quantified axon length and distribution within the C6 segment of the spinal cord. Both groups of rats showed a strong and persistent impairment in forelimb supination at 6 weeks after injury. Early result show both groups make a large-scale and sustained recovery of supination with the onset around the time of rehabilitation. Anatomical analyses are ongoing and will be compared with behavioral recovery. Preliminarily, timing does not seem to be a critical variable for combining motor cortex stimulation and rehabilitation.




**Disclosures:** **T.T. Bethea:** None. **J. Santos:** None. **H. Park:** None. **A. Sindhurakar:** None. **J. Carmel:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.14/JJ12

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** NIH Grant NS083666

CHNF Grant 316299

**Title:** NKCC1 contributes to exercise-dependent recovery of presynaptic inhibition after spinal cord injury

**Authors: *G. CARON**, B. DUFFY, M.-P. COTE
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**Abstract:** After spinal cord injury (SCI), an initial state of motor depression is often followed by a state of hyper-excitability. The decreased ability to depress spinal reflexes is attributed to increased gain of afferent feedback, loss of descending inhibition and reduced spinal inhibitory mechanisms. Indirect evidence suggests that presynaptic inhibition is decreased in chronic SCI individuals and that it is ameliorated by activity-dependent rehabilitation therapies. However, direct evidence of this phenomenon and the associated mechanisms in chronic SCI animal models remains elusive. Normal CNS inhibition relies on the opening of $GABA_A$ and glycine receptor-gated chloride channels. Chloride homeostasis is largely determined by the relative expression of two chloride transporters: the outward-rectifying KCC2 and the inward-directed NKCC1. Contrary to other neurons, primary afferents lack KCC2 and NKCC1 maintain high $[Cl^-]_i$. Consequently, the opening of $GABA_A$ receptors produces a depolarization that is associated with presynaptic inhibition, a mechanism by which afferents feedback is inhibited in a highly selective manner. After SCI, chloride homeostasis is disrupted in the lumbar spinal cord and leads to increased neuronal excitability associated with spasticity and hyperalgesia. We have previously shown that exercise alters chloride cotransporter expression in lumbar motoneurons which contributes to motor recovery after SCI. However, a disruption in chloride homeostasis also has the potential to impact sensory processing. Here, we explore the role of a change in NKCC1 expression in primary afferents on the level of presynaptic inhibition after SCI and physical activity. Adult Sprague-Dawley females underwent a complete spinal transection and were assigned to a sedentary group or a step-trained group. During a terminal experiment, DRPs and plantar H-reflexes were evoked by stimulating the tibial nerve with or without a conditioning stimulation to PBSt. Our results suggest that step-training increases presynaptic inhibition after chronic SCI as measured by increased DRP amplitude and facilitation. This increase was greatly diminished by blocking NKCC1 with bumetanide. Western Blot analysis revealed a step-training-dependent increase in the expression of NKCC1 in dorsal root ganglion that is correlated

with the increased DRP amplitude and the recovery of presynaptic inhibition. Together, these results provide direct evidence that restoring chloride homeostasis in primary afferents has the potential to restore presynaptic inhibition and improve sensory processing after chronic SCI.

**Disclosures: G. Caron:** None. **B. Duffy:** None. **M. Cote:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.15/JJ13

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** FINEP 01.12.0514.00

AASDAP

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**Title:** Locomotion training with closed-loop brain-machine interface and lower-limb functional electrical stimulation for complete paraplegic patients

**Authors: *A. SELFSLAGH**[1,2], S. SHOKUR[1], A. R. C. DONATI[1,3], D. S. F. CAMPOS[1], S. B. ALMEIDA[1,3], N. PADULA[1,4], H. BLEULER[2], M. BOURI[2], M. A. L. NICOLELIS[1,5,6,7,8]
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**Abstract:** Spinal cord injury (SCI) is a neurological deficit that impairs both motor and sensory pathways. In a recent work, we have demonstrated that long-term neurorehabilitation, integrating noninvasive brain-machine interfaces, tactile feedback and locomotion training with robotic gait trainer, lead to significant improvements in sensory and motor functions in patient diagnosed with complete paraplegia [1].
We present here a novel non-invasive neurorehabilitation protocol that combines brain-machine interfaces (BMI), functional electrical stimulation (FES) and tactile feedback. The protocol was tested with complete paraplegic patients (ASIA A/B) over a 12-month long training period. In a setup reproducing natural walking using a body weight support system device, the patients imagine moving their own legs to trigger the stimulation of their ipsilateral lower limb to

produce steps. As the sequence initiates, the patients receive tactile feedback on their forearm representing the swinging of the leg and the contact of the foot with the ground. Brain signals are recorded by 16 EEG electrodes centered over the legs sensory-motor area. Legs stimulation is applied through surface electrodes, mimicking synergic contractions of 16 lower limb muscles to reproduce a natural walking pattern. Tactile feedback is displayed on patients' forearm by means of arrays of vibrators.
Patients were able to control the BMI setup after a few training sessions. Using the BMI-FES setup they performed in average 70 steps per session; and a cumulated walking of up to 3000 steps per patient. We observed an increase in the travelled distance per session (from 25 to 55 m), as well as an important decrease in spasticity and muscle fatigue. As a result of the training, we observed neurological improvements below the SCI, and a significant increase in their functional walking (speed and cardiovascular conditioning).
Our work demonstrated the viability of a BMI-FES setup as rehabilitation tool for chronic complete paraplegics.
[1] A. R. C. Donati, S. Shokur, and E. Morya, "Long-term Training with a Brain-Machine Interface-Based Gait Protocol Induces Partial Neurological Recovery in Paraplegic Patients," *Sci. Rep.*, no. 6, 2016.

**Disclosures: A. Selfslagh:** None. **S. Shokur:** None. **A.R.C. Donati:** None. **D.S.F. Campos:** None. **S.B. Almeida:** None. **N. Padula:** None. **H. Bleuler:** None. **M. Bouri:** None. **M.A.L. Nicolelis:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.16/JJ14

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** NIH Grant K12HD073945

**Title:** Timing-dependent conditioning of deep dorsal horn neural circuits: Methodology for closed-loop control and implications for spinal cord injury-related neuropathic pain

**Authors: *J. G. MCPHERSON**
Biomed. Engin., Florida Intl. Univ., Miami, FL

**Abstract:** Spinal cord injury (SCI) results in altered neural activity in spinal sensory and motor circuits. Whereas activity-dependent reinforcement of inappropriate neural activity can lead to debilitating motor impairments and neuropathic pain, therapies that restore and reinforce natural, appropriate patterns of neural activity can significantly enhance recovery. Previous work has demonstrated that spinal motor circuits can undergo a type of activity-dependent plasticity that

resembles biphasic spike-timing-dependent plasticity (STDP). In STDP, the order and latency of firing between pre- and post-synaptic neurons determines whether synaptic output is potentiated or depressed. We have recently developed a pre-clinical intervention inspired by this phenomenon that uses intraspinal microstimulation (ISMS) to strengthen descending motor pathways that were spared by the SCI. We have shown that this approach can lead to substantial gains in motor rehabilitation that persist for weeks following discontinuation of stimulation. Because activity-dependent neural plasticity is also an integral component of pain processing, STDP-inspired approaches have a high potential to form the basis of neuromodulatory therapies for pain. In contrast to motor rehabilitation paradigms, we hypothesize that STDP-inspired depressive conditioning will be important for restoring and reinforcing natural neural activity in spinal sensory circuits. However, it remains unknown whether spinal sensory circuits can undergo timing-dependent changes in excitability.
Here, we present a closed-loop neural computer interface that can be used either to characterize basic timing-dependent properties of dorsal horn circuits or as the basis of a novel pre-clinical intervention for SCI-related neuropathic pain. All experiments were conducted in urethane anesthetized adult female Sprague-Dawley rats. We first show that salient non-noxious afferent activity can be discriminated in real-time from intramuscular EMG and used to trigger ISMS in deep dorsal horn circuits. We then show that noxious afferent activity can be discriminated in real-time from peripheral nerves and used as the ISMS trigger. Both triggers are important because the deep dorsal horn contains wide dynamic range neurons that process noxious and non-noxious inputs and are integral to the development and persistence of SCI-related neuropathic pain. By altering the latency and order in which ISMS is delivered relative to the arrival of the peripheral afferent volley, we use intraspinal recordings and spinal reflexes to systematically quantify conditioning mediated changes in neural excitability.

**Disclosures: J.G. McPherson:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.17/JJ15

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Travis Roy Foundation

1R21EB020318-01A1, NIBIB-NIH

**Title:** Paired motor cortex and cervical spinal cord electrical stimulation is safe and effective over six months in awake rats

**Authors: *A. PAL**[1], A. M. MISHRA[1], A. GARCIA-SANDOVAL[2], S. RATNADURAI-GIRIDHARAN[1], W. VOIT[2], J. B. CARMEL[1,3]
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**Abstract:** In our previous studies in anesthetized rats, motor cortex and cervical spinal cord paired electrical stimulation augmented motor function through converging descending motor and sensory afferent inputs into the spinal cord. Cervical spinal stimulation is challenging in awake animals due to narrow epidural space and large neck movement. We developed softening polymer-based electrode arrays (Fig. B), which are thin, flexible, and durable. These electrodes are stiff at room temperature and become supple after implantation into epidural space. We hypothesized that these spinal electrodes would be safe and effective for paired electrical stimulation in awake rats over months. Three sets of electrodes were implanted (Fig. A): spinal array electrodes over dorsal C5-C6, screw electrodes over motor cortex, and EMG electrodes in biceps muscle. We tested electrode impedance and spinal cord stimulation intensity required to provoke a motor evoked potential (MEP) over 6 months or until electrode failure. The effects of paired stimulation were tested in two ways. First, to test immediate effects of paired stimulation, we compared motor cortex evoked MEPs with and without subthreshold spinal stimulation delivered 10ms later. Second, to assess lasting effects of paired stimulation, we paired repetitively for 5minutes and measured cortical MEPs and spinal excitability (spinal MEPs and H-reflex) before and after pairing. The spinal arrays take the shape of underlying spinal cord, as shown by MRI. Electrode impedance was stable up to 6 months, with small increases in spinal cord MEPs. Subthreshold spinal stimulation caused more than threefold increase in cortical MEPs compared to only motor cortex stimulation. Repetitive pairing caused strong augmentation of cortical responses and spinal excitability that lasted for more than an hour after 5 minutes of pairing. Both immediate and lasting effects of paired stimulation were observed to the 6 months. Thus, we conclude that paired stimulation is safe and effective for chronic stimulation and suitable for testing in motor recovery after CNS injury.

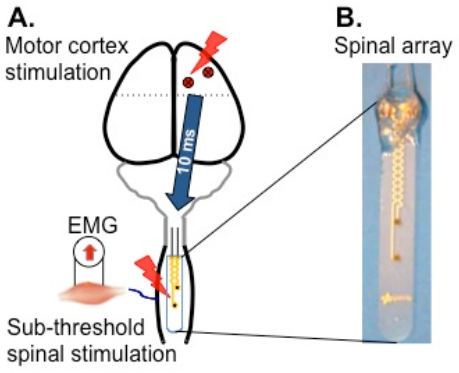



Figure: Paired motor cortex and spinal cord stimulation. (A) Paired stimulation paradigm and (B) Chronic spinal epidural array electrode.

**Disclosures:** **A. Pal:** None. **A.M. Mishra:** None. **A. Garcia-Sandoval:** None. **S. Ratnadurai-Giridharan:** None. **W. Voit:** F. Consulting Fees (e.g., advisory boards); Interim President of Qualia Medical, CTO of Syzygy Memory Plastics.. **J.B. Carmel:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.18/JJ16

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** FAPESP

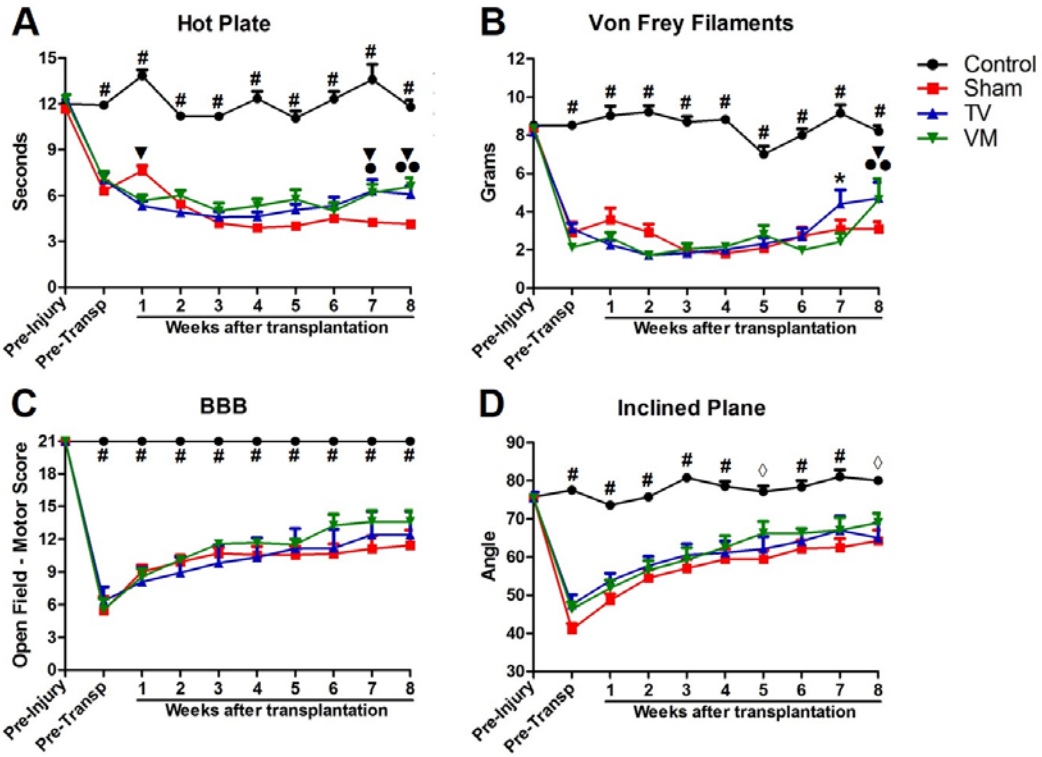
CNPq

**Title:** Improvement in pain sensation after transplantation of neuronal fetal progenitors into the injured spinal cord in the rat model

**Authors: *C. M. BATISTA**[1], E. D. MARIANO[1], F. ONUCHIC[1], C. S. DALE[2], A. F. CRISTANTE[3], J. P. OTOCH[4], M. J. TEIXEIRA[1], G. LEPSKI[1,5]
[1]Neurol., Univ. of São Paulo Med. Sch., Sao Paulo, Brazil; [2]Inst. of Biomed. Sci., Univ. of Sao Paulo, São Paulo, Brazil; [3]Orthopedic and Traumatology, [4]Surgery, Univ. of Sao Paulo Med. Sch., São Paulo, Brazil; [5]Neurosurg., Eberhard-Karls Univ., Tuebingen, Germany

**Abstract: Background and aims:** Neuropathic pain after spinal cord injury (SCI) is a complex condition which responds poorly to usual medications. Cell transplantation represents a promising treatment for it; nevertheless, the ideal cell type in terms of neurogenic potential and effectiveness against pain remains largely controversial. Here, we evaluated the ability of fetal neural stem cells (fNSC) to relieve chronic pain, as well as to promote motor recovery in the SCI impactor model. **Methods:** Adult Wistar rats were submitted to traumatic SCI using the NYU Impactor (drop height 25mm) at 9-10$^{th}$ thoracic level after laminectomy. After 10 days, the spinal cord was re-exposed and the animals received four intra-spinal injections of culture medium (sham group) or fNSC extracted from telencephalic vesicle (TV group, GABAergic precursors) or ventral medulla (VM group, serotonergic/ noradrenergic precursors). Cells were extracted from E/14 embryos. Behavioral assessment was performed weekly during 8 weeks. All animals were immunosuppressed by daily intraperitoneal injections of cyclosporine (10mg/kg) and received prophylactic oral administration of antibiotics (Sulfadoxin and Trimethoprin). **Results:** Hot plate test showed improvement in thermal pain sensitivity of ≈47.5% in the TV group in relation to sham group ($p<0.05$) at the 7th and 8th week after transplantation and an improvement of 45.9% ($p<0.05$) and 59.3% ($p<0,01$) at the 7$^{th}$ and 8$^{th}$ week, respectively, of the VM group in relation to the sham group. Mechanical allodynia, as assessed by von Frey filaments, improved 52.1% in the TV group ($p<0.05$) and 49.8% in the VM group ($p<0.01$) at the

8th week. BBB test failed to show a significant motor improvement in either VM group (19% of improvement, p=0.27) and TV group (8.5% of improvement, p=0.69) comparing to sham. In the inclined plane test also no difference across groups was noticed (VM group p=0.25; TV group p=0.88). **Conclusions:** Neuronal precursors from the TV and VM, once implanted into the injured spinal cord, are both able to alleviate pain, but fail to induce any significant motor recovery.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.19/JJ17

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** NIH Grant NS069765

Craig Neilsen Foundation (#297064)

**Title:** Upregulation of spinal 5HT1A receptor and its roles in bladder dysfunction after spinal cord injury

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**Abstract:** Normal lower urinary tract function requires the coordination of detrusor and external urethral sphincter activity during bladder filling and micturition. Experimental studies in animals have demonstrated a dense innervation of serotonergic fibers and the involvement of multiple serotonergic receptors in the spinal reflex circuit for voiding function. Spinal cord injury (SCI) above the lumbosacral level often leads to dysfunction of the lower urinary tract, including detrusor hyperreflexia, wherein bladder compliance is low, high baseline pressures are increased, and filling is accompanied by numerous non-voiding contractions (NVCs) referred to as neurogenic detrusor overactivity. Here, we investigate the expression level of the 5HT1A receptor in the L6-S1 segment of spinal cord as well as the role of 5HT1A receptor in regulating micturition using pharmacological interventions after T8 complete SCI in rats. Adult female rats were divided into two groups: (1) Sham control (T8 laminectomy only) and (2) T8 complete spinal cord transection. The observation period was two months after the original SCI. In anatomical analyses, we identified significant up-regulation of 5HT1A receptor expression in both gray and white matter of the L6-S1 segment after complete SCI. These animals with higher intensity of 5HT1A receptor also showed a higher number of NVC activities. In pharmacological studies, application of a selective 5HT1A receptor agonist (8-OH-DPAT) caused a reduction of NVCs and these effects could be reversed by subsequent application of a selective 5HT1A receptor antagonist (WAY100635). Interestingly, application of WAY100635 alone also resulted in inhibitory effects on NVCs with a reduced number and decreased amplitude, but increased the interval of NVC. These inhibitory effects on NVCs can be reversed by subsequent application of a beta-adrenergic blocker (propranolol). In addition, WAY100365 treatment decreased the coordination of activities between external urethral sphincter and detrusor, but increased the bursting duration and interval of sphincter bursting activity during the voiding period. These data suggest that 8-OH-DPAT may activate certain 5HT1A receptors that are silent following a SCI. On the other hand, WAY 100635 may block the constitutive activities of 5HT1A receptors but activate the beta-adrenergic sympathetic pathway, which in turn relaxes bladder activity. Together, the neuroplasticity of 5HT1A receptors can be a potential therapeutic target for treatment of bladder dysfunction after SCI.

**Disclosures: C. Lin:** None. **K. Li:** None. **R. Thalluri:** None. **Y. Lee:** None.

**Poster**

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**Location:** Halls A-C

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Mayo Clinic Center for Biomedical Discovery

**Title:** Diet induced obesity impairs neurobehavioral recovery after experimental spinal cord injury

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**Abstract:** Metabolic syndrome is a well-recognized risk factor for the development of cardiovascular disease, type 2 diabetes, and neurodegenerative conditions, but there is little information regarding its impact on recovery of function after spinal cord injury (SCI). This lack of knowledge exists despite the concern that cardinal features of Metabolic syndrome, including obesity, insulin resistance, hypertension, and a pro-inflammatory state could negatively impact the response of the spinal cord to injury and its capacity for regenerative repair. To address this gap in knowledge, we investigated the impact of systemic insulin resistance generated in adult mice by diet-induced obesity (DIO) on neurobehavioral outcomes in an experimental compression model of incomplete SCI. Ten-week-old female C57BL6/J mice were provided a regular diet, or one high in fat and sucrose (also referred to as a Western diet), for 7 weeks prior to experimental SCI. Mice continued on the same diets after SCI and were monitored weekly for locomotor recovery. Compared to mice consuming a regular diet, those with DIO demonstrated significant delays in locomotor recovery determined by the Basso Mouse Scale score and subscore, and the Inclined Plane test ($P < 0.05$, Two Way Repeated Measures ANOVA, Newman Keuls post-hoc test). Mice consuming a high fat diet also continued to lag behind their regular diet counterparts in these key motor outcomes 30 days post injury (dpi). To address potential mechanisms, we investigated changes in key markers of inflammation, astrogliosis and neural injury in the spinal cord after 7 weeks of consumption of a regular or high fat diet prior to SCI, and at 14 and 30 dpi, using immunochemical markers. Mice consuming high fat showed higher levels of glial fibrillary acidic protein (GFAP) in the spinal cord prior to SCI and in spinal segments above the injury epicenter at 14 dpi. Levels of Isolectin B immunoreactivity, a marker of microglial cells and monocytes were also higher in the spinal cord of mice consuming high fat prior to SCI. The spinal cord white matter of mice with DIO also showed reductions in the number of immature (Olig2+) and mature (CC-1+) oligodendrocytes prior to SCI, and these reductions in myelinating cells persisted at 14 and 30 dpi. Together, findings in this study identify DIO as a risk factor for impaired neurobehavioral recovery after experimental SCI and suggest the need to identify the mechanisms involved as potential new targets for therapy designed to improve outcomes in individuals with SCI.

**Disclosures:** **H. Kim:** A. Employment/Salary (full or part-time):; Yes. 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 R01 NS052741, NMSS RG4958, U24DK100469. Other; Mayo Clinic Center for Biomedical Discovery. **H. Yoon:** None. **I.R. Lanza:** None. **N.K. LeBrasseur:** None. **A. Matveyenko:** None. **I.A. Scarisbrick:** None.

**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

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**Program#/Poster#:** 501.21/JJ19

**Topic:** E.09. Spinal Cord Injury and Plasticity

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CNPq 300552/2013-9

**Title:** Ventral root crushing in mice: Time-course of glial reaction, synaptic changes and motoneuron survival

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**Abstract:** The spinal cord motoneuron (MN) is a unique element of the motor pathway, connecting the central nervous system (CNS) to the target muscle via the peripheral nervous system (PNS). MN cell body and axon's initial portion are located within the spinal cord, and most of the axon is present in the PNS. Due to such topography, lesions to the interface of CNS/PNS are especially severe since they represent a proximal axotomy, leading to 80% neuronal degeneration, within a couple of weeks. In patients, high energy trauma, such as motorbike accidents, can result in brachial plexus root avulsion or crush. Research on cellular and molecular changes in MNs and glial cells following proximal lesions has been carried out in cats and rats, mostly due to technical matters. However, proximal lesions to mice have not been performed in a standardized way. The present work, by the refinement of surgical technique and the use of appropriate surgical instruments, demonstrates the viability of crushing mouse ventral roots in a reproducible manner. Thus, we show herein the time course of neuronal degeneration, synapse retraction and glial reaction after ventral root crushing in C57BL/6J mice. For this purpose, 6-8 week old C57BL/6J mice were submitted to hemilaminectomy to expose the spinal cord lumbar segments (L4, L5 and L6). Once identified, ventral roots were crushed using a nº 5

forceps, for three times of 10 seconds. Operated mice were allowed to recover and were maintained for 7, 14 or 28 days after lesion. Following euthanasia, the spinal cords were collected to assess motoneuron survival by counting of Nissl stained sections, synapse loss (anti-synaptophysin) and glial reactivity (anti-GFAP and anti-Iba-1) via immunohistochemistry. Neuronal survival revealed 30% motoneuron loss seven days after lesion, which increased to 40 and 50% fourteen and twenty-eight days after lesion, respectively. Astrogliosis increased in a time-dependent manner, reaching six-fold upregulation by 28 days after injury. On the contrary, the microglial reaction was more intense in the acute phase after lesion (7 days), becoming reduced by 35% at day 28. The synaptic inputs were reduced by 35% nearby axotomized motoneurons already at day 7 after lesion, and such covering remained until 28 days post-injury. Taking together, the results herein demonstrate that ventral root crushing in mice provides robust data regarding neuronal loss and glial reaction, allowing future studies with transgenic strains that may, in turn, unveil strategies to improve motor recovery after proximal lesions.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.22/DP09/JJ20 (Dynamic Poster)

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** NIH Grant HL96750

**Title:** Neuroplasticity of glutamatergic neurotransmission at phrenic motor neurons following cervical spinal cord injury

**Authors: *S. RANA**[1], C. B. MANTILLA[2], H. M. GRANSEE[2], W.-Z. ZHAN[3], G. C. SIECK[3]
[1]Neurobio. of Dis., [2]Anesthesiol. & Perioperative Med., [3]Physiol. & Biomed. Engin., Mayo Clin., Rochester, MN

**Abstract:** Among patients with spinal cord injury (SCI), >50% involve the cervical spinal cord, with many cases resulting in paralysis of the diaphragm muscle and impaired ventilation. Importantly, most SCIs are incomplete with sparing of descending excitatory inputs to motor neurons. Animal models of incomplete SCI to the upper cervical spinal cord such as unilateral C2 hemisection (C2SH) are widely used to examine neuromotor control of breathing following injury. Excitatory premotor drive to phrenic motor neurons, emanating predominantly from the ipsilateral medulla, is primarily glutamatergic in nature and is mediated by various receptor subtypes, including ionotropic NMDA receptors. There is gradual recovery of rhythmic diaphragm muscle activity ipsilateral to injury over time, consistent with neuroplasticity and

strengthening of spared synaptic inputs to phrenic motor neurons. Following C2SH, the amplitude of respiratory-related diaphragm activity (generally recruiting smaller motor units) is reduced but diaphragm EMG activity during higher force, non-ventilatory behaviors (generally recruiting larger motor units) is only minimally impaired. Thus, there may be differences in cellular mechanisms of neuroplasticity at phrenic motor neurons that may depend on motor unit type. We hypothesized that NMDA mediated neurotransmission plays a role in spontaneous recovery of ipsilateral diaphragm muscle activity post-C2SH. We observe a progressive increase in overall NMDA receptor expression, as measured by mRNA expression of the obligatory NMDA NR1 subunit, in retrogradely labeled phrenic motor neurons post-C2SH. The time course of recovery correlates with changes in phrenic motor neuron NMDA receptor expression, and phrenic motor neuron NMDA receptor mRNA expression is greater in animals displaying recovery vs. those not recovered at 14 days post-C2SH. We further characterized the differences in expression of NMDA receptor mRNA in large vs. small phrenic motor neurons using fluorescent in-situ hybridization techniques. These studies directly address mechanisms underlying postsynaptic neuroplasticity at phrenic motor neurons and recovery after C2SH and support the role of glutamatergic NMDA signaling in recovery of diaphragm activity after cervical SCI.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

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**Support:** National Institutes of Health (P51 OD011107)

Department of Defense Spinal Cord Injury Research Program (SC090273)

Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

**Title:** Repair of a lumbosacral ventral root avulsion injury using GDNF-releasing nerve guidance channels to bridge tissue gaps between the spinal cord and avulsed ventral roots in rhesus macaques

**Authors: *N. P. BISCOLA**[1], J. H. NIETO[1], R. MARTIN[3], M. OHLSSON[5], K. L. CHRISTE[6], H.-Q. MAO[3], A. HOKE[4], L. A. HAVTON[2]
[1]Dept. of Neurol., [2]Departments of Neurol. and Neurobio., David Geffen Sch. of Med. at UCLA, Los Angeles, CA; [3]Dept. of Materials Sci. and Engin., [4]Dept. of Neurol. and Neurosci., Johns

Hopkins Sch. of Med., Baltimore, MD; [5]Dept. of Neuroradiology, Karolinska Hosp., Stockholm, Sweden; [6]California Natl. Primate Res. Ctr., UC Davis, Davis, CA

**Abstract:** Conus medullaris (CM) and cauda equina (CE) forms of spinal cord injury commonly result in paralysis, sensory impairments, and loss of bladder, bowel, and sexual functions. There are presently no treatments to reverse these neurological deficits. The present study investigated a new approach to promote axonal regeneration to reconnect spinal cord neurons with peripheral nervous tissues in a non-human primate model of CM/CE injury. For this purpose, biodegradable and trophic factor-releasing nerve guidance channels (NGCs) were used to bridge tissue gaps. The NGCs were comprised of electrospun polycaprolactone (PCL) tubes with an inner layer of aligned PCL nanofibers for topographical guidance and a PVA-collagen gel for controlled GDNF release (300ng/tube). Adult rhesus macaques underwent a unilateral L6-S3 ventral root avulsion (VRA) injury followed by repair of the L6 and L7 ventral roots. A glial cell derived neurotrophic factor (GDNF)-releasing NGC was placed as a bridge between the spinal cord and the avulsed L6 and L7 ventral roots (n=4). NGCs without trophic factor release were used as controls (n=4). Spinal cord and nerve root tissues were collected for morphological studies at 18 months post-operatively. Morphometric analysis of plastic embedded NGCs and nerve roots was performed using the free AxonSeg software. At 18 months post-operatively, both groups showed good integration between the bridging NGCs and the spinal cord as well as with the attached ventral roots. No graft rejections were detected. Cross-sections of GDNF-releasing NGCs showed a significantly higher percentage of overall tissue occupation (91.7±2.2%) compared to control NGCs (46.5±6.3%; $p<0.01$). Both groups showed a large number of myelinated axons in addition to fibrous tissues, Schwann cells, and blood vessels within the NGCs. The GDNF-releasing NGCs showed 3,230±669 myelinated axons, whereas the control NGCs showed 2,033±906 axons. There was no difference in axon numbers between the groups. There was no difference in fiber size or g-ratio between the groups. Electron microscopy of NGCs from both groups confirmed myelination of axons by Schwann cells as well as the presence of several unmyelinated axons with the NGCs. We conclude that the use of GDNF-releasing NGCs was well tolerated in non-human primates and promoted axonal regeneration in long-term studies. Trophic factor-releasing NGCs may be considered as a new repair strategy for bridging tissue gaps between the spinal cord and ventral roots after CM/CE injuries.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.24/JJ22

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Institute of Medical Science

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CIHR

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Krembil Research Institute

**Title:** Dual time course RNA-seq reveals level-specific neurovascular response after cervical and thoracic spinal cord injury

**Authors: *J. HONG**[1], M. CHAMANKHAH[1], A. BADNER[1], D. RIGHELLI[2], C. ANGELINI[2], M. FEHLINGS[1]
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**Abstract:** Traumatic spinal cord injury (SCI) is a devastating neurological condition that occurs primarily at the cervical (cSCI, > 65%) and thoracic (tSCI) levels. Despite the marked neurovascular distinctions of the two levels and strikingly positive response of cSCI to trial drugs such as cethrin compared to tSCI, the mechanisms driving level-specific heterogeneity between their respective milieu remains elusive. We posit that the increased vascularity and grey-white ratio of the cervical cord—relative to the thoracic—results in greater susceptibility to neurovascular disruption, ultimately manifesting a secondary injury of earlier onset, severity, and chronicity. A rat model of moderate clip compression injury was used to induce SCI at the C6-7 and T6-7 levels, with laminectomy-only animals serving as surgical controls. Following sacrifices at 3, 7, 14, and 56 days, samples were subject to RNA-seq, protein work, imaging, and immunohistochemistry. Results of RNA-sequencing revealed striking differences in the onset and temporal profile of astrocytic and pericytic neurovascular processes with canonic stat3-depen-dent gliotic markers—lcn2, gfap and serpina3n—being upregulated in the cervical cord across time. Further, 3D ultrasound and immunostaining revealed rapid tissue loss and hemorrhage starting as early as 3 days post-cSCI with increased gfap and cspg4 staining in the cord. Finally, Western blotting confirmed an increase in stat3-dependent gliotic markers accompanied by a loss of key blood-brain-barrier proteins tjp1 and ocln in cSCI across time. Taken together, this data demonstrates—for the first time—the level-specific heterogeneity of SCI, with cSCI having a quicker onset and chronicity compared to tSCI. Further, these results reconcile the potential reasons behind why preliminary tSCI-derived trial paradigms may not be suited--in both strategy and timing—to cSCI, and hopes to engage clinicians and scientists in the design and study of level-specific therapeutics.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

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**Title:** Transplantation of human inducible pluripotent stem cell-derived neural stem cells promotes locomotor recovery after cervical spinal cord injury

**Authors: Y. ZHENG**[1], C. GALLEGOS[1], H. XUE[1], S. LI[1], D. KIM[1], Y. LIU[1], *Q. CAO[2]
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**Abstract:** Human inducible pluripotent stem cells (hiPSC) offer tremendous potential for individualized patient- and diseased-specific therapy. Transplantation of hiPSC-derived neural stem cells (NSCs) could be one of the most promising novel reparative strategies to promote functional recovery after spinal cord injury (SCI). One of the major challenges to realize the full therapeutic potential of hiPSC for SCI and other neurological diseases is to direct hiPSC differentiation into desired neural stem or precursor cells in vitro and then purify these cells before transplantation. In this study, the recombined nestin-EGFP hiPSCs, in which EGFP cassette has been inserted to the nestin locus of hiPSC via homologous recombination, are induced for neural differentiation and GFP expressing NSCs are purified by FACS. The in vitro proliferation and differentiation of purified NSCs is examined using immunohistochemistry. The nude rats received unilateral C5 contusion injuries and grafts of hiPSC-derived NSCs, human fibroblasts or control medium at 2 weeks after SCI. The survival, differentiation and functional outcomes were analyzed by histology and behavioral tests. The purified NSCs expressed nestin, sox2 and sox1 but not iPSC markers, klf4, SSEA3, TR-1-60. The purified NSCs continued to proliferate in the presence of mitogen, FGF2 for a long time? and differentiated into neurons, astrocytes and oligodendrocytes in the respective specific differentiation conditions. Notably, robust survival of grafted NSCs was observed in all animals receiving grafts of purified hiPSC-NSCs at 2 months after transplantation. The majority of grafted NSCs localized in the spared spinal cord around the injured epicenter. Some grafted NSCs differentiated into NeuN+ mature neurons and more into doublecortin+ immature neurons. Some grafted NSCs, especially ones in

spared white matter, differentiated into GFAP+ astrocytes or APC+ oligodendrocytes. The volumes of spared white and gray matter are significantly increased in animals receiving NSC graft. More importantly, recovery of hindlimb locomotor function is significantly enhanced in animals receiving grafted hiPSC-derived NSCs. No teratoma formation was observed in any animals receiving hiPSC-derived NSCs. Our results suggest that hiPSC-derived NSCs have great therapeutic potential for SCI and other neurological diseases.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

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**Program#/Poster#:** 501.26/JJ24

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Title:** Local BDNF and minocycline delivery to the injured cervical spinal cord using an engineered hydrogel preserves diaphragmatic respiratory function

**Authors: B. GHOSH**[1], Z. WANG[2], J. NONG[2], M. W. URBAN[1], V. A. TROVILLI[1], M. C. WRIGHT[3], *Y. ZHONG[2], A. C. LEPORE[1]
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**Abstract:** We tested a novel biomaterial-based approach to promote repair and protection of neural circuitry that controls diaphragm activation by locally delivering brain derived neurotropic factor (BDNF) or minocycline hydrochloride (MH) to the injured spinal cord in a rat model of cervical contusion spinal cord injury (SCI). BDNF can be used to restore respiratory function via a number of potential repair mechanisms, including phrenic motor neuron (PhMN) protection, regrowth of descending respiratory-associated axons that are interrupted by cervical SCI, enhanced PhMN excitability, and preserved innervation at diaphragm neuromuscular junction (NMJ). However, widespread BDNF distribution resulting from conventional delivery methods such as systemic injection or intrathecal infusion can lead to inefficient drug delivery and adverse side effects. MH is a clinically-available drug that targets multiple secondary injury mechanisms via its anti-inflammatory, anti-oxidant and anti-apoptotic properties. However, MH is only neuroprotective at high local concentrations, which cannot be safely achieved by systemic injection. We developed a clinically viable approach for locally delivering MH and BDNF with controlled dose and duration: a hydrogel-based drug delivery system loaded with either polysaccharide-BDNF or polysaccharide-MH particles self-assembled by physical interactions. Intrathecal implantation of BDNF or MH gel after unilateral C4/5 contusion both robustly

preserved diaphragm function, as assessed by *in vivo* recordings of compound muscle action potential and electromyography amplitudes. However, BDNF did not decrease lesion size or degeneration of cervical motor neuron cell bodies, suggesting that its mechanism of action was not neuroprotection within spinal cord. Instead, BDNF gel significantly preserved diaphragm innervation by PhMN axons, as assessed by detailed NMJ morphological analysis and retrograde PhMN labeling from diaphragm using cholera toxin B. Furthermore, BDNF gel enhanced the serotonergic axon innervation of PhMNs that plays an important role in modulating PhMN excitability; this effect on 5-HT axon growth was not observed with MH. Unlike BDNF, MH gel decreased lesion size and cervical motor neuron loss, suggesting neuroprotection within cervical spinal cord. Our findings demonstrate that local BDNF and MH delivery via hydrogel represent effective and safe strategies to restore diaphragm function after SCI, though they exert therapeutic effects on respiratory neural circuitry via different mechanisms. Thus, co-delivery of both therapeutics can potentially be more effective than individual treatment.

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**Poster**

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**Title:** Neurotrophin-3 mediates descending afferents to lumbar motoneurons after an above-level spinal cord injury

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**Abstract:** After spinal cord injury (SCI), the surviving motoneurons, as the final common pathway for motor output, undergo profound dendritic atrophy and synaptic stripping from denervated supraspinal and propriospinal axons. In the present study, we investigated which specific descending pathways innervated the lumbar spinal cord after a T9 contusive SCI (Infinite Horizon with 0.4 mm displacement), and determined whether they contribute to neural synaptic reorganization and functional improvement after adeno-associated virus (AAV)-mediated neurotrophin-3 (NT-3) treatment for lumbar motoneurons. We demonstrated that, among various descending pathways, both the corticospinal tract and rubrospinal tract were almost completely disrupted at the lesion epicenter in both NT-3 treated and non-treated groups after SCI. Although no direct synaptic connections were found between these two pathways and lumbar motoneurons, the indirect cortico-motoneuronal and rubro-motoneuronal connections were still present via pseudorabies virus (PRV)-labeled propriospinal neurons, which were confirmed by electrophysiological recording. The spared proprio-motoneuronal connections were significantly enhanced, as evidenced by the observation of increased anterograde BDA-labeled propriospinal fibers and retrograde PRV-labeled propriospinal neurons after the NT-3 treatment. Using a propriospinal pathway-selective and reversible technique for blocking neuronal transmission, the beneficial effects of NT-3 treatment were significantly reversed in grid walking and rotarod behavior tests, revealing a critical role for the propriospinal-mediated motor control in response to NT-3 treatment. In addition, SCI with NT-3 treatment induced plastic changes of monoaminergic innervation of lumbar motoneurons, which may also contribute to functional recovery. These observations demonstrate that NT-3 treatment can modulate multiple spared descending pathways to maintain dendritic networks and synaptic plasticity of motoneurons after SCI, which could further benefit functional recovery.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.28/JJ26

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Swiss National Science Foundation

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Swiss Continence Foundation

**Title:** Anti-Nogo-A antibodies as a potential treatment for neurogenic lower urinary tract dysfunction after spinal cord injury

**Authors: *A. M. SARTORI**[1,2], M. P. SCHNEIDER[1], A. K. ENGMANN[1], A.-S. HOFER[1], M. E. SCHWAB[1], T. M. KESSLER[2]
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**Abstract:** Lower urinary tract dysfunctions arise in a majority of people with spinal cord injuries. Interestingly, the phenotype develops slowly over the first 2-4 months after the injury. The most frequent manifestation is detrusor sphincter dyssynergia (DSD), defined as bladder detrusor contraction with concomitant contraction of the urethral and/or periurethral striated sphincter muscle. DSD can result in high intravesical pressure and reflux of urine to the kidneys. Anti-cholineric drugs in combination with several rounds of daily self-catheterizations are the only treatment options today. The aim of this project was to investigate a potential therapeutic effect on the lower urinary tract of antibodies against the nerve growth inhibitor protein Nogo-A in spinal cord injured rats. Twenty Lewis rats were implanted with a port and tubing system to fill the bladder and monitor bladder pressure, as well as external urethral sphincter (EUS) electromyography electrodes, allowing for repetitive, simultaneous urodynamic measurement and recording of EUS activity in awake animals. A large, incomplete spinal cord injury was induced in all animals at the thoracic level 8. Afterwards, either control IgG antibodies (n= 9) or anti-Nogo-A antibodies (3 mg/week; n= 11) were infused intrathecally for 14 days. From 4 weeks after injury on, when DSD was fully developed in the rats, both bladder and EUS function were investigated. At 5 weeks after lesion, all animals were retrogradely traced from the EUS with Fast-Blue, followed by perfusion a few days later. Immunohistological analyses were performed at the lumbosacral spinal level. Four weeks after a severe but incomplete spinal cord injury, control antibody treated animals showed high intravesical pressures upon bladder filling and a micturition insmall droplets over a long time period, features that are typical of DSD. EUS EMGs showed high frequency activity during that period. In contrast, rats treated with anti-Nogo-A antibodies showed reduced maximal intravesical pressures during micturition by 50% compared to rats treated with IgG antibodies. EMG high-frequency activity of the external urethral sphincter during micturition was significantly lower in the anti-Nogo-A treated spinal cord injured animals, which is close to the level of intact rats. Immunohistological analyses are currently on-going to study the synaptic inputs of the sacral spinal cord sphincter motoneurons and the plastic reactions of spared descending fibers after the lesion and the two kinds of antibody treatments.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.29/JJ27

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Title:** The gigantocellular reticular nucleus is a key player for locomotor recovery after incomplete spinal cord injury

**Authors: *A. ENGMANN**, F. BIZZOZZERO, S. IMOBERSTEG, D. PFYFFER, M. P. SCHNEIDER, R. SCHNEIDER, O. WEINMANN, M. WIECKHORST, M. E. SCHWAB
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**Abstract:** The brainstem often has been thought to be specifically hardwired and bulbospinal fiber growth and plasticity after spinal cord injury have not been studied in great detail so far. Recent data suggest that following axotomy by spinal cord lateral hemisection in adult rats, the *gigantocellular reticular nucleus* (NRG), one of the main nuclei of origin of the descending reticulospinal tract, can sprout vigorously rostral to the lesion site (regenerative sprouting). Some of these severed fibers connect to propriospinal neurons, which run down the intact hemicord, thereby potentially relaying bulbospinal commands to denervated target areas [Filli et al. 2014]. In parallel, spared NRG axons on the contralesional side show sprouting in the lumbar spinal cord, projecting branches directly across the midline into the denervated hemicord (compensatory sprouting; [Zorner et al. 2014]). Animals and humans with this type of incomplete spinal cord injury have been described to show pronounced recovery of hind limb function.
This study aims at investigating the functional relevance of regenerative *vs.* compensatory NRG sprouting for behavioral recovery of locomoter performance, using intersectional viral genetics for introducing chemogenetic silencing tools. Detailed functional assessment of joint movements and limb kinetics during overground walking, wading and swimming under conditions, where one or the other of the plastic NRG projections were inactivated, revealed defined patterns of deficits in chronically recovered animals.
We here present causative data for the functional relevance of observed plastic adaptations of bulbospinal projections in the injured spinal cord for behavioral recovery. Moving from a purely correlative to a more causal understanding of the neuroanatomical processes contributing to functional recovery after spinal cord injury will be fundamental for a successful translation of novel treatment approaches from experimental studies to the clinics.

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**Poster**

**501. Spinal Cord Injury: Training, Rehabilitation, and Recovery**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 501.30/JJ28

**Topic:** E.09. Spinal Cord Injury and Plasticity

**Support:** Rick Hansen Foundation BCIP

**Title:** Further testing the robustness of “promising” neuro-protective drug candidates in a cervical hemi-contusion model of rats

**Authors: *W. T. PLUNET**[1], N. JANZEN[2], J. LIU[2], A. BEHRENS[2], E. RAFFAELE[2], O. SEIRA[2], L. MCPHAIL[2], W. TETZLAFF [2]
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**Abstract:** A significant number of FDA approved drugs have demonstrated efficacy in preclinical spinal cord injury (SCI). These studies predominantly used thoracic models and treated within one hour after injury. However, most human injuries occur at cervical levels (>65%), and such short windows of intervention used in animal studies are difficult to translate in human trials. We therefore created a team of research staff to assess the effects on functional recovery of the most promising FDA approved drugs when these are administered 3 hours after a cervical spinal cord hemi-contusion injury with the goal of finding robust treatments that could be taken forward into clinical trials.
In 5 experiments, we tested 9 different FDA approved drugs (riluzole, valproic acid, fluoxetine, metformin, inosine, rosuvastatin, acetyl-l-carnitine, glibenclamide, tamoxifen) that had been previously reported to improve functional recovery in SCI lab models.
None of the 9 treatments improved recovery compared to control groups in either a distal limb fine motor task (Montoya staircase: retrieval of food pellets from a staircase, or fruit-loop eating score), nor a proximal limb motor task (cylinder rearing task). We also did not observe any sparing of residual spinal cord tissue for the 6 treatments so far analyzed. However, mRNA expression changes in injured spinal cord tissue indicate appropriate changes in gene expression early after injury indicating the drugs are biologically active at the injury site.
In the light of this series of failures in our paradigm, we decided to reduce our injury force by 20% to 120 kdyn and to start treatment at 1 hour (n=19) and 3 hours (n=19) after cervical hemi-contusion injury (control n = 19). In the primary outcome of distal forelimb use there were no difference in the Montoya staircase task at any of the time points. Similarly, in the cylinder rearing task we did not observe robust differences among the groups at 3, 5 or 7 weeks after injury, however there was a trend for improvement in both the 1 and 3 hour glibenclamide treated groups.

As in previous replication studies, establishing robustness in preclinical models is challenging and possible reasons will be discussed.

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**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.01/JJ29

**Topic:** C.05. Neuromuscular Diseases

**Support:** Dutch Technology Foundation STW: 12803

ERC-Adv 320708: iConnect

**Title:** Sensorimotor activity during attempted finger tapping in late-stage ALS

**Authors: *E. G. PELS**, L. C. M. BRUURMIJN, E. J. AARNOUTSE, M. J. VANSTEENSEL, N. F. RAMSEY
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**Abstract:** Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease. It is characterized by a progressive degeneration of both upper and lower motor neurons resulting in paralyzed limbs, loss of speech and eventually locked-in syndrome. The median survival is 2-4 years from onset of symptoms, but can be prolonged with tracheostomy with invasive ventilation (TIV). Incremental evidence suggests that ALS is a multi-system disorder affecting also extra-motor areas, resulting in functional brain changes and behavioral changes (Shen *et al 2015*). A widely used technique to study functional changes within the brain is functional MRI (fMRI). So far, fMRI studies on the representation of limb movement in ALS patients have shown inconsistent results, although increased bi-hemispheric activation in pre- and primary motor cortex, more activation in motor learning related regions (cerebellum, basal ganglia) and recruitment of extra-motor areas such as primary sensory cortex and temporal and parietal regions were generally found. These findings indicate that the loss of motor neurons is compensated by the recruitment of other brain areas or reduced local inhibitory interneuron functioning. Importantly, these studies have been performed with relatively early-stage ALS patients who were still able to move their hand, and little is known about functional changes in the later stages of the disease. Here we report on functional activity in the sensorimotor cortex (M1/S1) of two people with late-stage ALS (revised ALS-FRS score: <5), who both received TIV and were unable to move their hands. M1/S1 activity was investigated using a block-design fMRI task in which the participants alternated attempted finger-tapping and rest. Participants

were scanned on 3T Philips MRI systems using PRESTO scans (TR/TE 22.5/31 ms; voxels 4mm isotropic). Data were compared with that of a group of healthy controls (execution of finger-tapping task). To allow easy visualization and to overcome individual anatomical variation, we used a novel method for normalizing M1/S1, based on anatomical landmarks (Bruurmijn *et al.* submitted). The results of both ALS patients showed significant activation in the hand region of M1/S1, in the same location as healthy controls executing the same movement. Additional activity was observed in face and foot regions, suggesting either additional engagement of these body parts during the attempt, or a reduced ability to activate the hand region selectively. In conclusion, we found relevant cortical activity in M1/S1 of people with late-stage ALS not able to move their hands, despite the significant loss of motor neurons as is known in ALS (Grolez *et al* 2016).

**Disclosures:** **E.G. Pels:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Funded by the Dutch Technology foundation STW with co-funding from Medtronic Europe.. **L.C.M. Bruurmijn:** None. **E.J. Aarnoutse:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Funded by the Dutch Technology foundation STW with co-funding from Medtronic Europe.. **M.J. Vansteensel:** None. **N.F. Ramsey:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Funded by the Dutch Technology foundation STW with co-funding from Medtronic Europe..

**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.02/JJ30

**Topic:** E.10. Motor Neurons and Muscle

**Support:** NIH Grant RO1 NS059947

**Title:** Size-dependent axon loss in the corticospinal tract in sporadic ALS patients with predominant upper motor neuron symptoms

**Authors: *F. SONG**[1], J. LIU[1], J. RAVITS[2], J. A. LOEB[1]
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**Abstract: Background:** Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that selectively involves both upper and lower motor neurons (MN). The mechanism by which both systems are involved is unknown. However, a common pathological finding in the spinal cord is corticospinal tract (CST) degeneration. We recently found a combination of myelin loss together with axonal loss in the CST tract where axons of different diameters are also

affected in patients with predominant upper MN signs. **Objectives:** In order to better understand the pathology, we compared the degree of axonal degeneration in the CSTs in ALS patients with predominant upper MN symptoms to patients with predominant lower MN symptoms in well-characterized postmortem cervical, thoracic, and lumbar spinal cord regions to determine the anatomical relationships of the connection between upper and lower MN systems in ALS patients. **Methods:** We developed quantitative methods to measure myelin and axon loss in three levels of the spinal cord. The degree of loss of axons of different diameters was measured and quantified in the CSTs as well as dorsal column regions as control in the different levels of spinal cords. **Results:** Patients with clinically predominant upper MN symptoms showed lateral and ventral CSTs degeneration. We found that all three spinal cord regions were affected in the CSTs but not the dorsal column. Quantification of axon density showed a loss of axons of both small and large diameter in the CSTs in ALS patients with predominant upper MN symptoms. Compared to ALS patients with predominant lower MN symptoms, we see a unique gradient of smaller diameter axon loss from lumbar to cervical segments in ALS patients with predominant upper MN symptoms. In ALS patients with predominant lower MN signs, we only see some loss of larger diameter axons. Moreover, significantly more microglial activation is associated with the severity of axon loss in the CST. **Discussion and Conclusions:** Our current findings show an 'All or None' effect of axon loss at all spinal cord levels of the lateral CST that is strongly associated with microglial activation. A 'Dying Back' of only small but not large diameter axons in patients with predominant upper MN symptoms. Our results suggest a selective vulnerability of axonal loss dependent on fiber size in ALS patients with predominant upper MN symptoms and that aberrant glioaxonal interactions in the spinal cord could contribute to axonal degeneration.

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**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.03/KK1

**Topic:** E.10. Motor Neurons and Muscle

**Title:** The impact of imperceivable vibration stimuli on the central nervous system

**Authors: A. D. PASSARO**[1], M. S. TENAN[1], C. A. HAYNES[1], *P. J. FRANASZCZUK[1,2]
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[2]Neurol., Johns Hopkins Univ. Med. Sch., Baltimore, MD

**Abstract:** Gaussian noise vibration stimuli has been shown to produce activation in specific contralateral and ipsilateral brain regions as well as decrease physiologic tremor. The present study used electroencephalography (EEG) to evaluate the neurological impact of an

imperceivable vibration stimuli on 4th finger tremor in 17 right-handed participants. Each participant applied force to a stimulated weapon with a trigger-like handle according to a visually-presented force-trace to guide them to a specific force level (20% of MVC) for a 30 second period. The force tremor was used to assess the behavioral effects of the perturbation. The vibration stimuli (Gaussian white noise) was applied during the middle ten second period only (10-20 s). The subsequent EEG analysis focused on the spectral components associated with the sensory perturbation by contrasting that condition with the identical sham condition in which no stimuli was applied.
A spectral decomposition of the 10 second sensory perturbation period as compared to the control condition yielded alpha power (8-13Hz) decreases in several channels over the posterior right of the scalp. Interestingly, the last 10 second period (20-30s) exhibited the most statistically significant differences between conditions with lower power in a narrow low gamma band (30-35 Hz) over the posterior right areas as well as an increase in power over the left lateral and left frontal brain regions (commonly associated with the contralateral primary somatomotor area) observed during the vibration stimuli condition. Behaviorally, the tremor associated with the trigger-pull trended lower during the vibration stimulation (repeated measures t-test p=0.067) but was not different from sham upon removal of the stimuli (repeated measures t-test p=0.649) . Previous studies have suggested that external noise elicits a stochastic resonance-like effect in the human tactile and visual sensory systems as well as decreases physiological tremor. The present study suggests that imperceivable vibration noise stimuli may increase force steadiness and has a definitive central nervous system response; however, these two phenomena may not be time-locked and the effects on the nervous system are longer lasting than the behavioral effects. Further study is required to understand how imperceivable sensory stimuli alters the time-course of motor adaptation and the creation of steady movement.

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**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.04/KK2

**Topic:** E.10. Motor Neurons and Muscle

**Title:** Altered motor axon excitability properties of the flexor carpi radialis following stroke

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**Abstract:** Spasticity and muscle hypertonia commonly develop following stroke, and may be related to motoneuron hyperexcitability. Neuronal plasticity associated with disease can be studied by examining biophysical properties of peripheral axons. Nerve excitability testing by threshold tracking provides an indirect assessment of axonal biophysical properties including ion channel conductance and the resting membrane potential in-vivo. In the present study, nerve excitability testing was completed in 6 men (30-65 y) who had a hemiparetic stroke 1-43 months earlier (mean 13.8 ± 6.9 months). Bilateral recordings of multiple motor axon excitability properties (strength-duration properties, threshold electrotonus, current-threshold relationship, and the recovery cycle) were made by stimulating the median nerve at the elbow and recording the compound muscle action potential over the flexor carpi radialis (FCR) muscle. Upper limb Fugl-Meyer scores ranged from 4-53 and wrist flexor Modified ashworth scores ranged from 0 to 1+. Mean (± SE) hand grip strength was reduced in the paretic compared to the non-paretic limb (4.5 ± 2.6 kg vs. 31.1 ± 4.7 kg, P = 0.001). There was no strong evidence for a change in the resting membrane potential in the paretic side axons. Threshold responses elicited by subthreshold polarizing currents (threshold electrotonus and current-threshold properties) were not different between limbs (P > 0.05), suggesting that internodal properties were unaffected following stroke. However, the mean strength-duration time constant, which reflects nodal persistent sodium conductance, was larger in the paretic compared to the non-paretic limb (0.438 ± 0.015 ms vs. 0.389 ± 0.016 ms (P = 0.05). In the recovery cycle, the relative refractory period and refractoriness at the 2.5 ms delay were also larger in the paretic limb; 4.06 ± 0.218 ms vs. 3.67 ± 0.198 ms (P = 0.003) and 52.2 ± 11 % vs. 30.3 ± 3.4 % (P = 0.09), respectively. There was a trend for the strength-duration time constant to be larger in persons with lower Fugl-Meyer scores (R = -0.7, P = 0.1).The results demonstrate limb differences in nodal properties, possibly reflecting increased persistent sodium currents in the paretic side axons. These preliminary findings suggest altered properties of the nodal membrane in FCR motor axons that may related to the development of spasticity and muscle hypertonia.

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**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.05/KK3

**Topic:** E.10. Motor Neurons and Muscle

**Title:** The effect of lower limb ischaemia on evoked potentials

**Authors: *J. M. BRADSHAW**, J. F. S. MILLWOOD HARGRAVE, P. S. SARAI, P. H. STRUTTON

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**Abstract:** Ischaemic nerve block (INB) of the limbs causes motor and sensory evoked potentials loss distal to the block site. Increases in motor evoked potential (MEP) amplitudes in muscles proximal to the ischaemia have been reported and it has been suggested that these are due to increased cortical excitability as a result of deafferentation of the limbs. Small increases in MEPs from contralateral muscles have also been noted. In order to further investigate the effect of ischaemia on cortical excitability and possible mechanisms, we performed an INB on the right calf. Nineteen healthy subjects received transcranial magnetic stimulation of the motor cortex and electromyographic activity of abductor hallucis brevis (AHB) and vastus lateralis (VL) muscles was recorded bilaterally. Somatosensory evoked potentials (SSEPs) were measured following electrical stimulation of the tibial nerve at the medial malleolus, distal to the INB. Near-infrared spectroscopy was used to measure regional tissue oxygen saturation ($rO_2$) at the calf and sole distal to the occlusion as a measure of the progression of peripheral ischaemia. We observed a significant increase ($p=0.008$ for VL, $p=0.007$ for AHB) in the amplitudes of MEPs in the contralateral muscles during ischaemia, in addition to expected decreases in MEPs of the ipsilateral distal AHB ($p<0.001$). However, there was no significant increase ($p = 0.076$) in the MEPs of the ipsilateral VL. SSEPs fell to an average of 41.29% of their baseline vs. 6.50% for MEPs at 30mins of ischaemia ($p<0.05$). These results suggest that increases in cortical excitability occur without loss of sensory input, indicating that complete deafferentation may not be the cause. It is possible that partial deafferentation may be sufficient to augment cortical excitability, or that an alternative mechanism may underlie these changes. Measures of $rO_2$ may provide a potential indicator of ongoing ischaemia and may be used as an adjunct to neurophysiological measurements. Further research is required to better understand the mechanisms underlying alterations in cortical excitability seen in ischaemic models of deafferentation.

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**Poster**

**502. Motor Neurons: Functional Relationships**

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**Program#/Poster#:** 502.06/KK4

**Topic:** E.10. Motor Neurons and Muscle

**Support:** University of Texas Grant - Undergraduate Research Fellowship

**Title:** Vastus medialis oblique activity is positively correlated with functional ability in patients with patellofemoral pain syndrome

**Authors: *R. T. PHAM**, Y.-L. PENG, D. GUPTA, L. GRIFFIN
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**Abstract:** Patellofemoral pain syndrome (PFPS) is the most common diagnosis of knee joint pathology. It diminishes a patient's capacity and desire to ambulate and limits ability to perform activities of daily life. It has been theorized that a weak vastus medialis oblique (VMO) causes the vastus lateralis (VL) to pull the patella laterally, causing friction and subsequent pain. The Anterior Knee Pain Scale (AKPS) is used widely to quantify physical ability and pain severity. The AKPS surveys the extent of discomfort during everyday activities (prolonged sitting, walking, general pain, stairs, limp, and support), more intense activities (running, jumping, and squatting), and the physiological effects of pain (flexion deficiency, abnormal patellar movement, swelling, and atrophy of thigh). The higher the score, the more able the subject is, with a maximum score of 100. Although the AKPS is commonly used, no studies have been done to evaluate the relationship between the AKPS score and the activation of the medial and lateral vastus muscles. The purpose of this study was to demonstrate the correlation between the total score of the AKPS and the activation amplitude of the VMO and VL during different tasks and force levels. Eight females with PFPS were recruited. The AKPS was administered and maximum voluntary contraction (MVC) force was determined by the average of the three MVCs. Participants then performed a ramp-up to three different target forces (25% MVC, 50% MVC, and 75% MVC) in two different tasks (isometric straight leg raise and isometric knee extension). The holding times were 10 sec for the 25% and 50% MVC, and 5 sec for 75% MVC. Surface electromyography (EMG) was used to measure muscle activation of the VMO and VL during the holding phase. Pearson correlation was used to determine the relationship between the total AKPS score and the normalized EMG activity of the VMO and VL, respectively. The EMG amplitude of the VMO had a relatively low, yet significant, positive correlation with the AKPS score during the 25% MVC straight leg raise task (25 ± 19% MVC, $p=0.03$, $r^2=0.3$) and the 50% MVC straight leg raise task (51 ± 30% MVC, $p=0.03$, $r^2=0.3$). However, there was no correlation between VL EMG amplitude to the AKPS score in all forces and tasks. The total score of the AKPS was positively correlated only with the VMO EMG during straight leg raise tasks at lower force levels which indicates that the more physically able the participants are, the stronger the VMO activation they have.

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**Poster**

**502. Motor Neurons: Functional Relationships**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.07/KK5

**Topic:** E.10. Motor Neurons and Muscle

**Title:** Cross-inhibition sharpens fast motor output in *C. elegans* locomotion

**Authors: L. DENG**[1], C. DOYLE[2], V. MARFIL[1], *G. HASPEL[1]
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**Abstract:** To achieve translocation, many locomotor systems produce alternation of antagonist muscle, including axial bending and limb alternation. Cross-inhibition is believed to be key to antagonistic alternation so that when a muscle is activated by the neural circuit, cross-inhibitory elements inhibit a counteracting muscle. Nineteen inhibitory GABAergic motoneurons (D-MNs) in *C. elegans* have been suggested to provide cross inhibition, based on their morphology and inhibitory effect on muscles. They each receive synaptic input from excitatory MNs and provide inhibition to opposing MNs and muscles. The activity of D-MNs during locomotion has not been reported but it is believed that cross-inhibition is key to undulatory dorsoventral muscle alternation in *C. elegans* during backward locomotion. However, we found that cross-inhibition is not necessary for slow antagonistic alternation, but it plays a crucial role in fast alternation. We use a combination of behavior analysis, optogenetics, and calcium imaging to clarify the role of the inhibitory D-MNs. We found that mutants that are deficient in GABA transmission so that cross-inhibition is missing, moved at lower frequency and slower translocation speed in both forward and backward directions. They can perform slow dorsoventral undulation as well as wild type. In contrast, they cannot move rapidly, for example to escape from noxious stimuli, neither backward nor forward. Moreover, we found that both forward and backward undulation frequencies of wild type animals each fall into slow and fast distributions, and that the frequencies of mutants overlap with the low frequency distribution of wild type. When mutant animals were exposed to noxious stimuli that would have induced fast forward or backward undulation in wild type animals, they contracted their posterior or anterior sections, respectively, exhibiting co-contraction of antagonistic muscle. Similar changes in locomotion behavior occurred when D-MNs were acutely inactivated with optogenetics. We recorded the neuronal activity of D-MNs, as well as the activity of excitatory MNs and muscle cells, during restricted locomotion using microfluidic channels that mimic natural shape of undulation so that all elements can be correlated in the same framework of undulatory phase.
Together, these finding support our hypothesis that cross inhibition sharpens the coordination of fast antagonistic alternation. The simple mode of locomotion and small neuronal network that can be comprehensively described and modeled, together with the availability of genetic and transgenic tools make *C. elegans* an exquisite model to further our understanding of motor networks.

**Disclosures: L. Deng:** None. **C. Doyle:** None. **V. Marfil:** None. **G. Haspel:** None.

**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.08/KK6

**Topic:** E.10. Motor Neurons and Muscle

**Support:** HKRGC-GRF grant (14106914)

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**Title:** Motor cortical activities in the animal model of Parkinson's disease

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**Abstract:** The primary motor cortex (M1) is responsible for motor execution and contributes to acquisition of new motor skills. Previous studies show that M1 layer V pyramidal neurons have increased burst firing and increased beta power in Parkinson's disease (PD) model. However, most studies have focused on recording extracellular activity *in vivo* or intracellular properties *in vitro* in M1. Properties of these neurons in intact subjects, like the *in vivo* intrinsic membrane excitability and synaptic inputs, which are important in understanding neuronal integration leading to their outputs, are less well addressed. We therefore applied *in vivo* whole-cell patch-clamp technique to record from neurons in M1, focusing on layer V. As a first step, we characterized the electrophysiological properties of these neurons in normal mature mice and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice under anesthesia. Neurons were approached, patched blindly and recorded for at least 20 mins. The depth of the neurons was recorded and confirmed by post-mortem biocytin avidin-biotinylated complex method that also revealed the neuronal morphology. Our data show that the intrinsic properties of the neurons, including the resting membrane potential, input resistance and membrane time constant, remain largely unchanged in MPTP-treated mice. Also, the averaged firing rates were unaffected. However, there is an increase in the number of spikes per burst and also a decrease in inter-burst intervals. The proportion of bursty neurons is also increased in MPTP mice. Subthreshold excitatory postsynaptic current (EPSC) and inhibitory postsynaptic current (IPSC) could also be recorded, which could provide insight into the mechanisms underlying changes in the firing patterns in M1 neurons observed in PD subjects.

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**Poster**

**502. Motor Neurons: Functional Relationships**

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**Topic:** E.10. Motor Neurons and Muscle

**Support:** NRF Grant 2014K1B1A1073720

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NRF Grat 2014R1A2A2A09052449

**Title:** Cultured motor neuron-based microfluidic platform for neural regeneration study

**Authors: *H. YOO**[1,2], H. JEONG[2], Y. CHO[2], S. HWANG[2], S. JUN[2,3]
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**Abstract:** Peripheral nerve injuries affect over 90,000 people worldwide every year. During several decades, due to the rapid development of electronics, implantable neural prostheses system is gaining a great attentions. Even though the electronic system has become highly functional and miniaturized, the interface between electrodes and nerve system is still a big limitation. It is mostly because the damaged nerves cannot maintain a stable connection with the electronics. For example, in order to control the artificial hand or leg with a person's intention, encoding the neural signal from the recovered motor neurons should be obtained for long time. In this study, we designed a cell culture platform to investigate how to regenerate motor neurons for a stable connection with electrodes. SU-8, a photoresistor, was used to make a mold (master) with positive relief patterns using soft lithography. Structure made by molded PDMS (polydimethylsiloxane) covers a commercial planar type microelectrode array to utilize electrical recording and stimulation functions. Primary motor neurons from embryonic 14-day gestation ICR mouse spinal cord was dissociated and seeded in the platform. Microchannels between the chambers provide high fluidic resistance that leads to directional neuron growth. In order to confirm successful neuronal growth and regeneration, we attempted to detect the activity of neurotransmitter simultaneously. When neurons grow along the microchannels, we detected acetylcholine from the terminal of the motor neuron using electrochemical method. This study indicates that the microfluidic platform can be an in-vitro neural recovery model.

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**Poster**

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**Title:** Improving the sensitivity and stability of detecting proximal muscle MEPs through high-density EMG

**Authors: *F. A. MUSSA-IVALDI**[1], D. DE SANTIS[2], B. AFSHARIPOUR[3], N. L. SURESH[5], W. Z. RYMER[4], L. M. ROGERS[6]
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**Abstract:** Proximal muscles in the arm have a broader cortical representation compared to forearm and hand musculature. They are characterized by higher threshold to TMS motor evoked potentials even in healthy individuals. As a consequence, few studies have evaluated the excitability of corticospinal projections to muscles of the arm and the shoulder. However, muscles such as biceps, triceps, deltoid and trapezius are of particular interest after cervical SCI, both for evaluating the level of the lesion and the efficacy of therapeutic interventions.
In this work we propose to use TMS in combination with high-density surface EMG (HD-sEMG) to obtain a more detailed picture of the evoked activity in the proximal muscles of the upper limb. Our hypothesis is that, not only would HD-sEMG provide a spatial map of TMS-evoked activity in the muscle, but it would also detect MEPs with higher sensitivity compared to standard bipolar surface EMG recording. To the best of our knowledge, only one group has previously adopted HD-sEMG with the aim of studying spatial selectivity of TMS in the forearm musculature.
Here, we compared MEPs obtained with bipolar recording and recording from grids of electrodes when evaluating recruitment curves (RC) and cortical mapping of proximal arm muscles. Single-pulse TMS was delivered to the contralateral motor cortex using a neuro-navigated Nexstim eXimia NBS stimulator via a 70 mm figure-of-eight coil while the subject was at rest. Upon identification of the hotspot and resting motor threshold (RMT) via bipolar recordings, we varied the intensity of the stimulation in percentage of 10% RMT above and below the RMT for obtaining the RC. Subsequently, we moved the coil along a grid of 5x5 $mm^2$ projected virtually

onto the cortical surface in order to record MEPs to 120% RMT across different stimulation sites. We repeated the procedure using an 8x8 grid of electrodes interspaced by 8.5 mm. The protocol was repeated in separate days to verify the stability of measures extracted by the grid. We were able to elicit MEPs in all the tested muscles. We evaluated the peak-to-peak amplitude of the response and the MEP onset latency across the grid of electrodes. Our results suggest that HD-sEMG allows detecting MEPs at lower stimulation intensities, and with a more consistent sigmoid RC shape, compared to bipolar electrodes. Indeed, we could exploit the spatial resolution of the grid to achieve a topographical picture of MEPs propagation in the muscle and for identifying more excitable regions. Given the promising results, we will take the next steps towards evaluating the reliability of this technique for studying proximal muscles both in uninjured and SCI individuals.

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**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.11/KK9

**Topic:** E.10. Motor Neurons and Muscle

**Support:** NIDILRR Grant 90RE5013

**Title:** Alteration of surface electromyogram patterns after botulinum toxin injection in stroke survivors

**Authors: *B. AFSHARIPOUR**[1,2], S. CHANDRA[1,2], W. Z. RYMER[1], N. L. SURESH[1]
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**Abstract:** Botulinum toxin is widely prescribed by physicians for managing spasticity post stroke. In an ongoing study, we examine the spatial pattern of muscle activity in muscles of stroke survivors before and after receiving botulinum toxin over the course of several weeks. We hypothesize that botulinum toxin alters muscle electrophysiology by disrupting fiber neuromuscular transmission in an inhomogeneous manner and we seek to detect these changes using grid surface electromyography (sEMG). We recorded sEMG signals from Biceps Brachii (BB) in two chronic stroke survivors using 16x8 surface EMG grid with 8.5mm inter-electrode distance. The grid covered the short and long head of BB. We recorded from both impaired and contralateral sides of our stroke survivors during sustained, non-fatiguing, voluntary contraction at maximum voluntary contraction (MVC) and at 50%MVC. All recorded signals were preprocessed (power line attenuation, 10-500Hz bandpass filtering). We calculated the root mean

squared (RMS) value of each channel for a 5s constant force and presented it as 16x8 RMS map. We compared the RMS maps of pre and post-botulinum toxin sessions. We observed discernible changes in the RMS pattern of BB muscle after receiving botulinum toxin. A significant decrease in sEMG amplitude (RMS) was observed for all 128 channels during MVC contractions. We also found significant differences between the spatial pattern of pre and post botulinum toxin RMS maps at 50%MVC. Botox chemically denervates the muscle fibers around the injection site(s). A reduction in the number of muscle fibers contributing to the force generation results in a significant force reduction at the elbow joint of the botulinum toxin recipients. We further postulate that dysfunctional muscle fibers that are not generating action potentials alter the distribution of sEMG in a non-uniform manner over the skin surface. In conclusion, we have observed the evidence of alteration of the amplitude and pattern of muscle activity after botulinum toxin injection. Further analysis and study will also include motor unit analysis and mapping.

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**Poster**

**502. Motor Neurons: Functional Relationships**

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**Program#/Poster#:** 502.12/KK10

**Topic:** E.10. Motor Neurons and Muscle

**Support:** NIDILRR-90RE5013

**Title:** Effect of botulinum-toxin on motor unit activity in stroke survivors

**Authors: *S. CHANDRA**, B. AFSHARIPOUR, N. SURESH, W. Z. RYMER
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**Abstract:** Use of Botulinum-toxin is often utilized by physicians to reduce muscle spasticity in stroke survivors. This toxin is locally administered to the affected muscle site as an intramuscular injection to inhibit hyperactivation of the spastic muscle. The reduction of muscle spasticity is achieved by blocking neuromuscular transmission, thereby also affecting voluntary muscle activation and in turn, muscle control. We hypothesize that Botulinum-toxin also affects motor unit (MU) functional properties such as motor unit recruitment threshold and motor unit firing rate. By decomposing surface electromyogram signals (sEMG) from Biceps Brachii, we address the effect of Botulinum-toxin on MU activity of the muscle.
Experimental surface electromyogram recordings were performed on three stroke survivors after a thorough clinical assessment. The force and sEMG signals were recorded during an isometric, non-fatiguing elbow flexion under kinematic constraints. Visual feedback of a trapezoidal force

trajectory was provided to the subjects. EMG data were recorded using Delsys Sensor Arrays, which are equipped with special 5 electrode pins. We also recorded surface EMG with 4 bipolar sEMG electrodes. The 4 bipolar sEMG electrodes recorded signals from long and short heads of the distal portion of Biceps Brachii, Brachioradialis and Triceps Brachii. All the data were normalized with a Maximal Voluntary Contraction (MVC) before they were decomposed to individual motor unit action potentials. Multiple experimental trials were performed at different contraction level varying from 30% to 60% of the MVC.
We found variation in motor unit recruitment patterns and the firing rates for the post Botulinum-toxin sessions comparing to baseline recordings (before Botulinum-toxin injection). Along with MVC, the peak to peak amplitude of sEMG of the affected muscle in the impaired side also showed significant decrease in value. Recruitment thresholds also decreased for the higher threshold motor units in the post injection sessions. A compression in the initial recruitment range was observed for the post Botulinum-toxin sessions even though in both the cases the "onion skin" pattern was preserved. A greater variation of firing rates was evident in post Botulinum-toxin sessions. Compared to the pre-injection sessions, the post injection sessions show decreasing trend in the firing rates across all forces. In summary, motor unit control is potentially altered following botulinum toxin injections in muscles that exhibit spasticity.

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**Poster**

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**Topic:** E.10. Motor Neurons and Muscle

**Support:** NIDILRR Grant SI16000119

NIDILRR Grant 90RE5013

**Title:** Acute intermittent hypoxia-induced neuroplasticity in individuals with incomplete cervical spinal cord injury

**Authors: *M. S. SANDHU**[1], B. AFSHARIPOUR[2], A. ADEKUNLE[2], S. ANASTASOPOULOS[2], W. Z. RYMER[2]
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**Abstract:** Spinal cord injuries (SCI) disrupt the pathways between brain and spinal cord, resulting in impairment of motor control and loss of independent mobility. Most SCIs are

incomplete, however spontaneous plasticity, mediated via the spared spinal pathways is often insufficient to restore normal function. One unique approach to induce plasticity in spared spinal networks is via brief exposures to reduced oxygen levels, also known as acute intermittent hypoxia or AIH. This protocol has been demonstrated to increase voluntary force generation at the ankle joint as well as improve locomotor function in persons with SCI. Whether AIH induced neuroplasticity is equally prevalent in spinal motor pathways regulating upper limb musculature is not known. Accordingly, we tested the hypothesis that AIH will augment upper limb neuromotor function in individuals with incomplete SCI. A randomized, blinded, placebo-controlled and crossover study design was used. We measured isometric elbow flexion and extension strength during maximal voluntary contraction (MVC) in 8 individuals with chronic, incomplete cervical SCI before and 60 minutes after a single session of AIH (15, 90-second episodes of 10% oxygen). Results were compared with trials when subjects received sham hypoxia (15, 90-second episodes of 21% oxygen). Electromyographic activity was also recorded from the biceps brachii and triceps brachii muscles using a 128 channel high density grid. We found that force output during isometric MVC at the elbow flexion and extension changed by 43 ± 13% and 51 ± 22%, respectively, following AIH. In contrast, force output during flexion and extension changed by 13 ± 8% and -4 ± 7%, respectively. The change in flexion and extension strength correlated with increased activation of biceps brachii and triceps brachii. These results demonstrate the potential of AIH to enhance volitional upper limb strength in persons with incomplete SCI. This modality could eventually be developed to induce spinal plasticity as an adjunct to bolster the effectiveness of superimposed rehabilitative training in SCI patients.

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**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

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**Program#/Poster#:** 502.14/KK12

**Topic:** E.10. Motor Neurons and Muscle

**Support:** Falk Trust at the Rehabilitation Institute of Chicago

Davee Foundation grant to the Rehabilitation Institute of Chicago

**Title:** Analysis of motor unit action potential shape and power spectral changes in surface EMG of hemiparetic stroke survivors

**Authors: *N. L. SURESH**[1], X. HU[3], B. JEON[4], W. Z. RYMER[2]
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**Abstract:** Muscular weakness is a major impairment limiting motor function following a hemispheric stroke. The objective of this preliminary study was to examine potential motor unit (MU) structural change in paretic muscle of stroke survivors as a measure by which to assess neural and/or biomechanical mechanisms of paresis. A surface electromyogram (sEMG) recording and decomposition system was used to record sEMG signals and extract single MU activities from the first dorsal interosseous muscle (FDI) of two hemiparetic stroke survivors. To characterize MU structural change, an estimate of the motor unit action potential (MUAP) amplitude and duration was derived using spike triggered averaging of the sEMG signal. We also derived parameters from EMG power spectral analysis, such as frequency range and median frequency and made comparisons between data obtained from the affected and contralateral sides of stroke subjects. Our preliminary results reveal MUAPs with systematically smaller amplitude and longer duration in the paretic muscle compared with the contralateral muscle of two tested stroke subjects with moderate and severe impairment. Preliminary results also show significant differences in the median frequency values between the stroke and contralateral side of our three tested stroke subjects. These preliminary results suggest reduced MU size and a reduction in the conduction velocity in post-stroke paretic muscle which could be contributing factors to existing muscle weakness. The sEMG recording and decomposition system combined with our spike triggered averaging technique has the potential to provide an assessment tool for muscular weakness post-stroke.

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**Poster**

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**Topic:** E.10. Motor Neurons and Muscle

**Support:** Joint Science and Technology Office, Medical S & T Division
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NIAID AOD12058-0001-0000

**Title:** Designer ubiquitinase targeting botulinum neurotoxin a is transgenically expressed and forestalls paralysis

**Authors: *T. RUSSO**[1], P. M. MCNUTT[1], A. B. BRADFORD[2], J. MACHAMER[3]
[1]USAMRICD, Gunpowder, MD; [2]US Army Med. Res. Inst. of Chem. Def, Gunpowder, MD; [3]US Army Med. Res. Inst. of Chem. Def., Gunpowder, MD

**Abstract:** Botulinum neurotoxin serotype A (BoNT/A) is an extremely potent toxin that specifically cleaves the presynaptic protein SNAP-25, blocking cholinergic neurotransmission. The resulting flaccid muscle paralysis becomes fatal once respiratory muscles are intoxicated. Currently, the only FDA-approved treatment for botulism is passive immunization with antitoxin, which removes the neurotoxin from circulation. However, antitoxin is ineffective once toxin translocates to the presynaptic compartment. Our goal is to design a novel treatment that blocks or reverses the catalytic activity of the botulinum neurotoxin light chain (LC) of serotype A within the presynaptic terminal, thereby providing a countermeasure that can be utilized following symptomatic onset. Here we describe the initial validation of a bifunctional designer ubiquitinase (DesUbA), designed to that both block LC catalytic activity and to ubiquitinate LC, accelerating its proteolysis. DesUbA is composed of the single-chain antibody B8 VHH and the ubiquitin ligase domain, TrCP. In preliminary studies conducted in neuroblastoma cells, DesUbA has been shown to both ubiquitinate LC/A as well as block the catalytic activity of LC/A. To test DesUbA performance in a physiological model, C57BL/6J mice were genetically modified to express YFP-DesUbA using a pan-neuronal Thy1.1 promoter. Stable breeding lines were established and TFP-DesUbA expression was confirmed in the brain and peripheral nervous system, including motor neurons and neuromuscular junctions. To functionally validate the acute effects of DesUbA on LC/A activity, isometric contractions were measured *ex vivo* in phrenic nerve-hemidiaphragm (PNDs) intoxicated by BoNT/A. Transgenic PNDs showed greater than 50% delay in times to median paralysis and full paralysis as compared to preparations from wild-type mice, suggesting that DesUbA decreases LC/A activity. The effects of DesUbA expression on LC/A persistence *in vivo* are currently under investigation using novel behavioral models of systemic botulism and local paralysis.

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**Poster**

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**Program#/Poster#:** 502.16/KK14

**Topic:** E.10. Motor Neurons and Muscle

**Support:** OCAST grant HR-14-023 to J.M.D.

**Title:** The effects of altered stretch reflex sensitivity on motor unit recruitment

**Authors: A. BARRERA-CURIEL**, *Z. K. POPE, R. J. COLQUHOUN, J. A. HERNANDEZ-SARABIA, J. M. DEFREITAS
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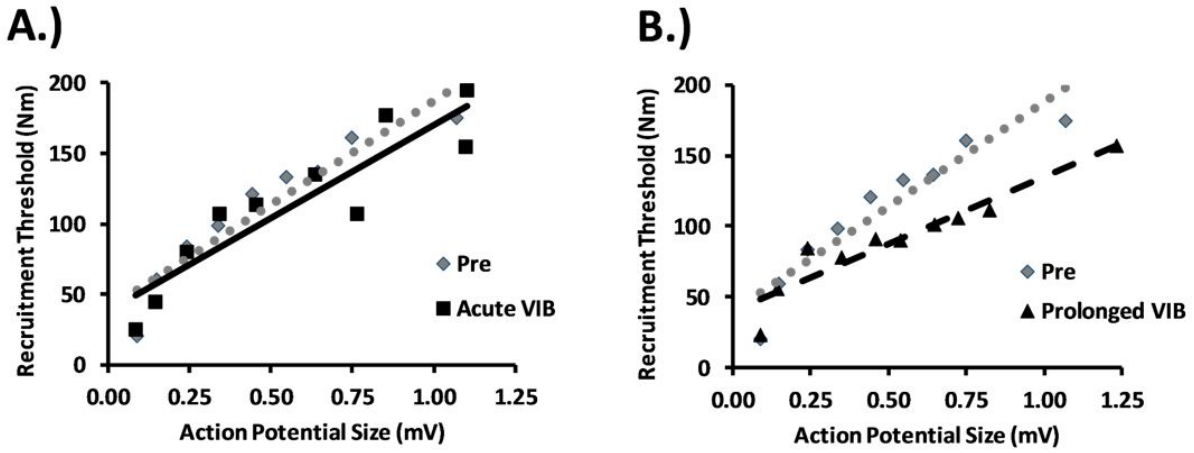
**Abstract: INTRODUCTION:** Motor unit activation is controlled through the integration of descending command and afferent feedback. It is well-established that vibration applied to the muscle manipulates the excitatory synaptic input to muscle spindles by either facilitation (acute vibration for less than 30 seconds) or depression (prolonged vibration for > 10 minutes) of spindle function. Despite evidence that muscle spindles alters motor unit behavior, the direct influence of muscle spindles on motor unit recruitment thresholds (RT) during maximal efforts remains untested. **PURPOSE:** To examine the effects of altering stretch reflex sensitivity on maximal motor unit properties. **METHODS:** 5 healthy men (23 ± 4yrs) and 8 healthy women (23 ± 11) were included in this study. A crossover design was utilized, where each participant performed 1 maximal knee extension under 3 separate conditions: 1) control; 2) acute vibration, applied during the contraction; and 3) prolonged vibration, applied for ~20 min prior to the contraction. Multi-channel EMG was recorded from the vastus lateralis during each contraction and decomposed into the constituent motor unit action potential trains. RT was characterized as the force level (Nm) at which each motor unit started firing. **RESULTS**: 1,120 motor units were detected overall. No significant differences in maximal RT were found from the control to either the acute conditions (p = 0.186) or prolonged conditions (p = 0.089). However, when expressing each motor unit's RT as a function of its action potential size, prolonged vibration significantly altered the slope (p = 0.032, Figure B), but acute vibration had no effect (p = 0.608, Figure A). **CONCLUSION**: Motor unit recruitment threshold decreases when muscle spindle function is depressed, suggesting that higher-threshold motor units are recruited earlier during maximal contractions when muscle spindle sensitivity is altered.

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**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.17/KK15

**Topic:** E.10. Motor Neurons and Muscle

**Title:** Recurrent laryngeal nerve regrowth post-injury: A temporal study of neurotrophic factor expression

**Authors: S. DODHIA**[1], *I. HERNANDEZ-MORATO[2], M. MONTALBANO[2], J. MARTINEZ[3], M. PITMAN[2]
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**Abstract:** The recurrent laryngeal nerve (RLN) innervates the intrinsic laryngeal muscles. The exquisite coordination between abductor and adductor muscles of the vocal folds is controlled by two pools of motoneurons. They are located in the nucleus ambiguus within the brainstem that supplies the larynx through the RLN. Injury of the RLN may occur during cervical or cardiothoracic surgery, and leads to vocal fold paralysis affecting vital functions like respiration, deglutition and voice production. Regenerating axons grow toward the laryngeal muscles, but due to non-selective reinnervation, the recovery of the vocal fold movement is typically absent. In previous works, we identified different neurotrophic factors whose expression is coordinated with the timing of axonal reinnervation of the larynx. Two such factors were Glial Derived Neurotrophic Factor (GDNF) and Netrin-1 (NTN-1). In this study the expression of GDNF and NTN-1 in denervated abductor and adductor muscles was analyzed with the mRNA translation of their receptors in the RLN and the brainstem. As laminin α1 (LAMA1) has been shown to change NTN-1 mediated growth cone attraction to repulsion, the expression of this protein in the laryngeal muscles was also studied.
Eighty-four female Sprague-Dawley rats underwent transection of the right RLN and were sacrificed at 1, 3, 7, 21, 28 and 56 days post injury. Ipsilateral posterior cricoarytenoid, lateral and medial thyroarytenoid muscles were collected and the total mRNA and protein were isolated for the determination of GDNF, NTN-1 and LAMA1 expression. Motor axons and motor end plates were immunostained to determine the timing of laryngeal reinnervation. GDNF and NTN-1 receptor expression was also studied in the brainstem and the axonal growth cones by immunohistochemistry and in situ hybridization.
The overexpression of GDNF and NTN-1 in the abductor and adductor laryngeal muscles correlated with the expression of their receptors within the nucleus ambiguus at different time points. LAMA-1 overexpression in the laryngeal muscles was also identified. This is a novel finding not previously described in any model of nerve injury.
Our findings suggest that expression of GDNF, NTN-1 and their receptors are chronologically

correlated with the laryngeal reinnervation. LAMA-1 overexpression may be a RLN axon guidance factor as it is known to induce repulsion of regenerating growth cones when associated with NTN-1 expression. Future study of the specific role of GNDF, NTN-1, and LAMA-1 may be helpful to better understand their function, with the goal of manipulating these neurotrophic factors to promote selective reinnervation with return of vocal fold function.

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**Poster**

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**Topic:** E.10. Motor Neurons and Muscle

**Support:** DOD Grant W81XWH-15-1-0229

**Title:** Does follistatin augment skeletal muscle fiber recovery following moderate periods of denervation?

**Authors: *M. S. SHALL**[1], J. E. ISAACS[2], S. MALLU[3], G. PATEL[4], M. A. FEGER[4]
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**Abstract:** Every year there are many nerve injuries that result in significant disability. The surviving motoneuron axons that do regrow to the muscle target are often re-innervating small, weakened, and compromised muscle fibers. The rapid degeneration of denervated muscle fibers following nerve injury seems to be related both to disuse and to a loss of trophic support and feedback normally provided by the intact axons. One approach to prevent atrophy is to facilitate the normal physiologic anabolic shift that occurs in the muscle fibers with re-innervation.
Some research on muscle mass regulation has focused on myostatin, a member of the TGF-β superfamily of signal transduction proteins that regulate muscle mass by inhibiting muscle regeneration. Elevated myostatin serum levels (acting as muscle inhibitors) have been linked to muscle wasting conditions such as AIDS or prolonged bed rest. Additionally, myostatin's protein reducing effects, though seen in all muscle fibers, is most prevalent in type IIb muscle fibers.
In light of the obvious therapeutic potential of manipulating myostatin related pathways for muscle regeneration, an intensive search has been underway for effective myostain antagonists. Follistatin has emerged as one of the most promising. Follistatin influences muscle regeneration at several levels including directly inhibiting myostain, stimulating muscle fiber hypertrophy and hyperplasia, and increasing both muscle fiber protein and myonuclei. Transgenic mice over-expressing follistatin exhibit faster muscle healing following muscle injury as demonstrated by

greater myofiber regeneration, less intra muscular fibrosis, and “superior” muscle progenitor cell formation.
The objective of the study is to determine potential augmenting effects of follistatin on strength, mass, and muscle fiber composition recovery of re-innervated muscle following moderate and long periods of denervation. Preliminary data shows that FS Protein is observed to induce muscle hypertrophy as seen by the increase in animal weight, muscle weight and the twitch force when compared to sham group. Muscle fibers expressing myosin heavy chain type II isoforms tended to be larger in the FS protein treated muscles compared to control animals.

**Disclosures:** **M.S. Shall:** None. **J.E. Isaacs:** None. **S. Mallu:** None. **G. Patel:** None. **M.A. Feger:** None.

**Poster**

**502. Motor Neurons: Functional Relationships**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 502.19/KK17

**Topic:** E.10. Motor Neurons and Muscle

**Support:** NIH 094450

NJCBIR CBIR16IRG032

**Title:** Optogenetic muscle activation to restore whisker movement after facial nerve lesion in mice

**Authors: A. BANDI**[1], A. UPADHYAY[1], H. CHANG[1], R. SAKHUJA[1], S. YIANTSOS[1], T. J. VAJTAY[1], C. R. LEE[1], *D. J. MARGOLIS[3,2]
[2]Cell Biol. and Neurosci., [1]Rutgers, The State Univ. of New Jersey, Piscataway, NJ; [3]Cell Biol. & Neurosci., Rutgers Univ., Piscataway, NJ

**Abstract:** Motor nerve damage can lead to complex functional changes in the denervated muscle, including atrophy and hypersensitivity, that can severely impact the restoration of movement. The temporal progression of denervation-induced changes in nerve and muscle function have been challenging to investigate experimentally. We used non-invasive peripheral optogenetic stimulation (Park et al., 2016, Peripheral optogenetic stimulation induces whisker movement and sensory perception in head-fixed mice, eLife, e14140; experiments performed under isoflurane anesthesia) in four transgenic mouse lines expressing channelrhodopsin-2 (ChR2) in either facial nerve or mystacial pad muscles to track changes in light-evoked whisker movements before and after facial nerve transection. Before nerve transection, graded whisker protractions were evoked by increasing light (460 nm) intensity or duration in muscle-expressing mice (Emx1-ChR2, PV-ChR2, and ACTA1-ChR2). By contrast, optogenetic activation of the

facial nerve (Chat-ChR2 mice) resulted in stereotyped, all-or-none, strongly adapting whisker protractions. After nerve transection, longitudinal probing of the distal cut end of the nerve in Chat-ChR2 mice revealed loss of movement within approximately 24 hours, defining a time window of functional denervation. Longitudinal probing of optogenetic muscle activation over 14 days revealed functional changes beginning after the functional denervation, including a reduction of retractions (Emx1-ChR2 mice), an increase in large-amplitude, non-adapting protractions, and increased sensitivity to low intensity stimuli (Emx1-ChR2, PV-ChR2, and ACTA1-ChR2 mice). In additional experiments, we used timed stimulation of retraction and protraction in attempt to reproduce aspects of natural whisking kinematics. After nerve transection, optogenetically induced naturalistic whisker movements were paradoxically improved, largely because of the denervation-induced reduction of adaptation. Our results indicate that peripheral optogenetic stimulation can be used to probe the time course and functional changes of nerve and muscle function after denervation that influence the ability to restore naturalistic whisker movements of denervated muscle. Our results have implications for the potential use of optogenetics for restoring movement in a therapeutic context after nerve damage.

**Disclosures: A. Bandi:** None. **A. Upadhyay:** None. **H. Chang:** None. **R. Sakhuja:** None. **S. Yiantsos:** None. **T.J. Vajtay:** None. **C.R. Lee:** None. **D.J. Margolis:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.01/KK18

**Topic:** F.01. Neuroethology

**Support:** Nipissing University

**Title:** Manipulation of the social environment alters activity and body morphology of Dugesia dorotocephala

**Authors: L. GOODRIDGE**, A. STILLAR, A. WEEKS, *M. J. SAARI
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**Abstract:** Planaria, *Dugesia Dorocephala,* appear to be behaviourally sensitive to their social environment. Singly housed planaria show reduced activity and increased environmental “scanning” in comparison to group housed planaria. The purpose of this study was to explore activity and body morphology of planaria exposed to four different social environments: singly housed, groups of five, and a group of ten in 5 ml of modified Montjuic salt solution. The fourth group consisted of ten planaria housed in 50 ml of the salt solution. *WormLab* (MBF Bioscience) was used to analyze video files of ten planaria from each of the environments. All groups were

videotaped at day 1 of the experiment and left undisturbed except for water changes which took place every 2nd day. The planaria were individually videotaped once more on day 7. Activity and body morphology measures were collated for the first and the second minute of the videotape. This yielded a mixed $SPF_{4.2}$ design with ten planaria per housing environment. ANOVA indicated a significant effect of Social Environment on speed of swimming and a significant Social Environment by Minute interaction on path length. Surprisingly, body morphology (length, width, and area) varied significantly as a function of Minute. The results confirm the behavioural sensitivity of planaria to their social environment and suggest that body morphology may provide a novel measure of adaptation. (Supported by Nipissing University).

**Disclosures: L. Goodridge:** None. **A. Stillar:** None. **A. Weeks:** None. **M.J. Saari:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.02/KK19

**Topic:** F.01. Neuroethology

**Support:** East Carolina University division of Research and Graduate Studies fund to F.I.

**Title:** The effects of social status on dopaminergic regulation of neural circuit activation and behavior

**Authors: *K. CLEMENTS**[1], T. MILLER[1], E. JI[2], F. ISSA[1]
[1]Biol., East Carolina Univ., Greenville, NC; [2]UCLA, Los Angeles, CA

**Abstract:** Social hierarchies permeate the animal kingdom and are crucial for maintaining social communities through proper allocation of resources. Our aim is to address the neural bases of social regulation using zebrafish (*Danio rerio*). Zebrafish form hierarchies of socially dominant and subordinate fish. They produce a well-characterized escape behavior that is mediated by the activation of Mauthner neurons. We used a non-invasive technique of recording field potentials that enable the monitoring of the escape and swim circuits to determine if there were differences between fish of different social status. Our results showed that there was a social status-dependent effect in the activation of the two competing neural circuits and their behaviors. We found that subordinates favored escape over swim while dominants favored swim over escape. We hypothesized that differential activation of these two behaviors and their underlying circuits are affected by social experience through mediation of the dopaminergic system. To test our hypothesis we first augmented dopamine (DA) through injection of L-DOPA. We observed that the significant difference in escape behavior between the two social phenotypes was diminished, suggesting a social status-dependent regulation of dopamine on the escape circuit. Second, whole brain gene expression analysis showed significant upregulation of the dopamine transporter (dat)

in dominants and downregulation of the dopamine receptor 1b (drd1b) in subordinates. There were no significant differences in gene expression of drd2a, drd2b or drd3. We investigated the status-dependent differences in DA receptor expression by pharmacologically injecting DA receptor agonists and antagonists. We found that blocking the drd1b shifted dominant behavior to favor escape over swim, resembling the subordinate behavior pattern. In addition, we observed that antagonizing drd3 lowered subordinates' probability of escape with no effect on dominants. Finally, neither application of drd2 agonist nor antagonist yielded significant effects. Taken together, these results suggest that social status can shift the activation of competing neural circuits mediated, in part, through the balance of DA supply regulated by dat and interpretation of DA by differences in drd1 and drd3 expression and signaling, respectively.

**Disclosures: K. Clements:** None. **T. Miller:** None. **E. Ji:** None. **F. Issa:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.03/KK20

**Topic:** F.01. Neuroethology

**Title:** Social regulation of the endocannabinoid system and modulation of the escape and swim circuits in zebrafish (Danio rerio)

**Authors: *S. A. ORR**, T. H. MILLER, F. A. ISSA
Biol., East Carolina Univ., Greenville, NC

**Abstract:** Social status-dependent modulation of neural circuits has been investigated extensively in vertebrate and invertebrate systems. However, the effect of social status on shifting the activation between competing neural circuits is poorly understood. Zebrafish (*Danio rerio*) form stable social relationships that consist of socially dominant and subordinate animals. Once the social hierarchy is formed, social status-dependent differences in behavior patterns emerge. Here, we investigated the role of the endocannabinoid system (ECS) in regulating the activation of the swim and escape circuits. Our aim was to investigate how the ECS facilitates the transition between swim and escape circuits in socially dominant and subordinate animals. Endocannabinoids act as retrograde signaling molecules between neurons, and are implicated in inhibition of both excitatory and inhibitory neurotransmission via retrograde binding of the cannabinoid 1 receptor (CB1R). A previous study revealed a novel role for the endocannabinoid 2-Arachidonoylglycerol (2-AG) in modulating the switch in activation between the swim and startle circuits in zebrafish. The ECS displays remarkable plasticity and can be easily up- or down-regulated by targeting CB1R function. To better understand how social status regulates the ECS and its effects on circuit activation, we studied the effects of AM-251, a CB1R reverse agonist, in regulating the status-dependent differences in swim and escape behavior. First, we

show that dominant and subordinate animals display significant differences in locomotor behavior as dominance is established. Subordinate animals startle more readily in response to auditory stimuli, while dominants swim at a higher frequency than subordinates. Secondly, pharmacological blockage of the CB1R via injection of AM-251 suggests that locomotor behavior in subordinate fish is more susceptible to ECS modulation, and that behavior in dominants is relatively more resistant to modulation. Finally, hindbrain gene expression results suggest that ECS genes are differentially expressed according to social status in that DAGL, the enzyme responsible for synthesizing 2-AG, is downregulated in subordinate zebrafish compared to dominants and social isolates (control). However, no differences in CB1R or MGL expression were observed between dominants and subordinates. Our results support the notion that the ECS is socially regulated and involved in mediated changes in relevant social behaviors.

**Disclosures: S.A. Orr:** None. **T.H. Miller:** None. **F.A. Issa:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.04/DP10/KK21 (Dynamic Poster)

**Topic:** F.01. Neuroethology

**Title:** Imaging of neural activity in the forebrain of adult zebrafish during social affiliative behavior

**Authors: *K.-H. HUANG**[1], K. KITAMURA[2], M. SCHEBESTA[3], F. SERLUCA[3], T. BOUWMEESTER[3], R. FRIEDRICH[1]
[1]Friedrich Miescher Inst., Basel, Switzerland; [2]Tokyo Univ., Tokyo, Japan; [3]Novartis Inst. for BioMedical Res., Basel, Switzerland

**Abstract:** Social affiliation with conspecifics is a behavior shared by many vertebrates. Zebrafish show robust shoaling behavior in adults that emerges gradually during development. We found that adult zebrafish approach movies of conspecifics but that this behavior attenuates rapidly during repeated movie presentations. Zebrafish carrying mutations in shank3B and fish expressing a dominant-negative shank3B construct, however, exhibit a sustained behavioral response to repeated movie presentations. To investigate the neuronal correlates of these behaviors we established a closed-loop, 3D virtual-reality (VR) approach where adult zebrafish are head-fixed and navigate in a virtual environment that includes movies of conspecifics. Activity patterns in the dorsal forebrain were imaged during behavior by two-photon calcium imaging at single-cell resolution. A subset of neurons showed activity that was correlated to the onset and offset of swimming events. Other neurons responded to perturbations of the VR such as interruptions or reversals of the coupling between motor behavior and the VR. Interestingly, a specific subset of neurons in forebrain regions Dc (possibly homologous to mammalian

isocortex) and Dm (presumably homologous to parts of the amygdala) increased their activity when the animal approached movies of conspecifics. These results are beginning to elucidate neuronal representations of social information and behavior in wild-type zebrafish and in genetic disease models.

**Disclosures: K. Huang:** None. **K. Kitamura:** None. **M. Schebesta:** None. **F. Serluca:** None. **T. Bouwmeester:** None. **R. Friedrich:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.05/KK22

**Topic:** F.01. Neuroethology

**Support:** LA Board of Regents RCS Grant #LEQSF(2013-16)-RD-A-02

National Science Foundation IOS-1456004

**Title:** Sexually-relevant visual and chemosensory signals induce distinct behaviors and brain activation patterns in the social African cichlid, Astatotilapia burtoni

**Authors: *K. FIELD**, C. T. MCVICKER, K. K. JOHNSON, K. P. MARUSKA
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**Abstract:** Across vertebrates, females are often senders of potent chemical signals that provide information important for coordinating reproductive events. In several fish species, these chemical signals can induce robust reproductive behavioral responses in male receivers. How the brain processes these sexually-relevant signals to elicit these behaviors, however, remains poorly understood. Here, we used the highly social African cichlid fish, *Astatotilapia burtoni*, to investigate how sexually-relevant chemical and visual signals from gravid (full of eggs) females influence behavior and brain activation patterns in dominant males. We presented both chemical (control water or gravid female-conditioned water) and visual (no fish control or gravid female) signals either alone or together and found that males need sexually-relevant visual signals to engage in stereotypical courtship behaviors such as body quivers, waggles, and leads into the spawning territory. However, the number of courtship behaviors was greater when males were dually exposed to visual and chemical signals from females, compared to either sensory signal alone. When a female visual signal was absent, males showed increased swimming and overall activity in response to female-conditioned water compared to control water, suggesting that female-released chemosensory signals may stimulate male searching behavior and motivation. Importantly, we also tested anosmic (olfactory ablated) males to demonstrate that this behavior is primarily mediated by the olfactory system rather than gustation. Using the immediate early gene

*cfos* as a proxy for neural activation, we also found that brain regions of the social decision making network show differential activation when dominant males are exposed to chemical and visual signals together compared to exposure of either sensory signal alone. For example, the ventral part of the ventral telencephalon (homologous in part to mammalian lateral septum) shows more activation in response to sexually-relevant visual signals regardless of whether chemical signals are present or not. In contrast, the dorsal part of the ventral telencephalon (homologous in part to mammalian nucleus accumbens) shows greater activation to sexually-relevant chemical signals regardless of whether visual signals are present or not, and the preoptic area has the greatest activation when chemical and visual signals are presented together. These data provide insight on distinctions between brain regions involved in olfactory processing itself from those involved in integrating multiple sensory modalities to elicit appropriate social behaviors.

**Disclosures: K. Field:** None. **C.T. McVicker:** None. **K.K. Johnson:** None. **K.P. Maruska:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.06/KK23

**Topic:** F.01. Neuroethology

**Title:** The behavioral effects of taurine in aggression of female crayfish, Procambarus clarkii

**Authors: *C. M. MECCA**, B. N. THOMAS, R. F. WALDECK
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**Abstract:** Crayfish will engage in aggressive behavior when confronted by a competing species. Once finished, these confrontations leave crayfish behaviorally effected, referred to as the loser effect (Moore, 2007). When a crayfish repeatedly wins its confrontations, its chances for winning increase, while a loser will continue to lose (Moore, 2007). Although the social behaviors of crayfish have been studied, it is unclear as to not only, what mechanisms are active in determining a confrontation, but also, what mechanisms are controlling the effects after confrontation. Taurine, an amino acid, may be beneficial in understanding aggressive behavior in crayfish (Galler et al., 1990). It is also understood that taurine is essential for the function and development of skeletal muscle and the central nervous system (Picones et al., 1992). In this experiment, the influence of taurine on the losing crayfish in fights between two female crayfish, *Procambarus clarkii*, was studied. Female crayfish were paired by size and then fought twice without drugs to determine the loser. After losers were given taurine, crayfish were fought twice again. All losing crayfish remained losers after administration of taurine. It was observed that there are additional characteristics in female confrontations that are not reported in male crayfish.

The aggression of crayfish given taurine was suppressed after drug administration. Losing female crayfish which had received taurine also had an increase in tail-flip frequency after being drugged with taurine. This might suggest that taurine acts on the regulatory loop in the tail that normally inhibits the tail-flip behavior (Wine and Krasne, 1972).

**Disclosures: C.M. Mecca:** None. **B.N. Thomas:** None. **R.F. Waldeck:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.07/KK24

**Topic:** F.01. Neuroethology

**Support:** NSF IOS 11471172

**Title:** Socially induced sensorimotor filtering plasticity in female African cichlid fish Astatotilapia burtoni

**Authors: M. ADELMAN**, A. CHEN, H. NEUMEISTER, *T. PREUSS
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**Abstract:** African cichlid fish *Astatotilapia burton*i have long been used as a model system for investigation of socially induced neuroplasticity. *A. burtoni* males alternate between dominant (DOMm) and territorial, and subordinate (SUBm) and non-territorial social status. We recently showed that male startle escape behavior and sensorimotor filtering abilities (pre-pulse inhibition, PPI) depend on social status. Specifically, SUBm show reduced PPI as compared to DOMm, suggesting that social defeat drives PPI plasticity. Interestingly, when housed without the males, female *A. burtoni* establish a male-like social hierarchy, with DOM females (DOMf) demonstrating territorial and aggressive behaviors towards SUB females (SUBf). However, the effect of social status on startle behavior and PPI in females is not known. Here we asked if DOMf and SUBf housed in female-only communities will demonstrate socially induced differential PPI comparable to their male DOM and SUB counterparts. In addition, since females in gender-mixed communities (COMf) are not frequently subjected to DOMm aggression, we also hypothesized they will not show PPI deficits. To test for PPI, COMf (N=10), DOMf (N=9) and SUBf (N=13) were exposed to a startling (pulse), preceded by a non-startling acoustic stimulus (prepulse), and responses were scored based on the presence of a startle response. Trials were conducted with the prepulse/pulse interstimulus interval (ISI 50ms). Preliminary results showed a trend toward reduced PPI effect in SUBf (51.9% +/- 6.8 SEM) as compared to DOMf (71.9 % +/- 7.0 SEM) which approached significance (p=0.072; independent samples t-test). The baseline startle rates were similar in the two groups. In addition, we found similar PPI effect in COMf (68.8% +/- 8.4 SEM) and DOMm (70.7% +/- 11.8 SEM) with no differences in baseline

startle rates. Taken together, these results suggest that social defeat may indeed drive PPI plasticity independent of gender, and that higher PPI observed in DOMm, COMf and DOMf might represent the default in this species.

**Disclosures:** **M. Adelman:** None. **A. Chen:** None. **H. Neumeister:** None. **T. Preuss:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.08/KK25

**Topic:** F.01. Neuroethology

**Support:** Ministry of Education, Science, Technology, Sports and Culture of Japan, Grant-in-Aids for Scientific Research (C), grant No. 22570079

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**Title:** Interneurons in the primary auditory center of the honeybee brain responsive to air vibration pulses as elicited during waggle dance communication

**Authors:** ***T. WACHTLER**[1], A. KUMARASWAMY[1], K. KAI[2], H. IKENO[3], H. AI[2]
[1]G-Node, Dept. Biol. II, Ludwig-Maximilians-Universität München, Planegg, Germany; [2]Dept. of Earth Syst. Sci., Fukuoka Univ., Fukuoka, Japan; [3]Sch. Hum. Env. Sci., Univ. Hyogo, Himeji, Japan

**Abstract:** Honeybees use the 'waggle dance' to communicate the location of nectar sources to their hive mates (von Frisch, 1967). During the waggle dance, the dancer produces trains of vibration pulses, which are detected by the follower bees via Johnston’s organ on the antennae. To uncover the neural mechanisms underlying the encoding of distance information in the waggle dance follower, we investigated morphology, physiology, and immunohistochemistry of interneurons arborizing in the primary auditory center of the honeybee (Apis mellifera). We

identified and categorized 119 vibration-sensitive interneurons based on morphology and responses to vibration stimuli. Three major interneuron types - the local interneuron DL-Int-1, the output neuron DL-Int-2, and Bilateral DL-dSEG-LP - showed specific GABA immunoreactivity and responded with different spiking patterns to trains of waggle dance-like vibration pulses applied to the antennae. We developed new methods for reconstruction and comparison of morphologies, and investigated the GABAergic local interneuron DL-Int-1 further, specifically its age-related adaptations of physiology and morphology. DL-Int-1 neurons from mature honeybees were morphologically different from those from young honeybees, showing region specific changes to dendritic density. DL-Int-1 also showed significantly stronger inhibition and post inhibitory rebound in mature foragers, further supporting the important role of inhibition in processing waggle dance signals. Our results suggest a disinhibitory network for encoding and processing the duration of vibration pulse trains in the primary auditory center of the honeybee.

**Disclosures:** **T. Wachtler:** None. **A. Kumaraswamy:** None. **K. Kai:** None. **H. Ikeno:** None. **H. Ai:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.09/KK26

**Topic:** F.01. Neuroethology

**Support:** NSF CAREER 1551526

**Title:** Modeling visual perception, learning, and memory of wood ants navigating in naturalistic environments

**Authors: *A. J. MENDOZA**[1], D. D. LENT[2]
[1]Biol., California State Univ. Fresno, Fresno, CA; [2]Biol., CSU Fresno, Fresno, CA

**Abstract:** A number of experiments have revealed how different visual features are used to guide familiar foraging routes in wood ants. Using these data, we have developed algorithms to extract visual features that ants use for guidance from panoramic scenes. Through simulation we have characterized how visual cues that ants use are extracted, prioritized and stored during navigation. A foraging model was created in MATLAB to simulate navigation in a procedurally generated environment where the visual cues could be precisely characterized. In these environments, our algorithms extracted and stored the visual cues that were available during a single Levy walk foraging event. Following a random foraging event, the success on subsequent foraging bouts using the stored information was examined. When we examined subsequent foraging walks we found the success of the simulated ant in finding the goal location using only

a particular cue or a combination of cues depended on two factors - the length of the route and decay rate of information in a memory network. To further explore this we simulated the Levy walk foraging event over various sampling points (100-10000) and implemented linear or exponential decay in the networks storing the information. Our data suggests that the optimal strategy is to sample and store between 1000 and 2000 points along the foraging route, independent of scale, with a network subjected to exponential decay. These parameters resulted in a stored representation that allowed the simulated ant to best find the goal on subsequent foraging bouts. We then produced several novel random foraging walks with the same goal location. The subsequent walks for these foraging events had similar success demonstrating sufficient information was stored and resulted idiosyncratic foraging routes due to the varied information encountered during the random walk. Additionally, we explored how multiple subsequent walks updated and modified memory to produce more robust walks over time. Lastly, we compared the success of subsequent of the model when foraging in sparse and cluttered environments. The results of these simulations have provided insight into the mechanisms involved in prioritization and perception of visual information, it supports that ants need only processes relevant cues intermittently and they do not continually process visual information. Additionally, it has let us investigate how learning and storage of spatial information can be optimized in simple networks and nervous systems.

**Disclosures: A.J. Mendoza:** None. **D.D. Lent:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.10/KK27

**Topic:** F.01. Neuroethology

**Support:** Andrews University Faculty Grant

**Title:** Behavioral and neuronal responses in male-exposed female cricket Acheta domesticus

**Authors: *B. A. NAVIA**, C. R. KENT
Dept. of Biol., Andrews Univ., Berrien Springs, MI

**Abstract:** Syllable period-selective phonotaxis in female cricket *Acheta domesticus* as well as the corresponding response of neural elements (such as the L1, L3 and ON1 neurons which influence phonotaxis) have been the focus of multiple studies. Such previous studies, have reported a degree of individual variability in phonotactic behavior..However, obvious differences in their responses based on age are typical for this species. The described behavioral and neuronal responses were correlated, and ranged from selective to unselective in both young and old females respectively. All of these studies have used virgin females raised in isolation. The

current project investigates the possible influence in the phonotactic and neuronal responses of male-exposed females of different ages. We hypothesized that the presence of males would significantly reduce phonotaxis by females to model calls. However, preliminary results reveal an increase in behavioral response and a reduction in syllable period-selective phonotaxis. Furthermore, in contrast with previous studies, we did not observe any correlation between female age and phonotactic responsiveness. Regardless of age, male-exposed females seemed not to discriminate between attractive and unattractive model calls. Additionally, call intensity may also affect syllable-period selective phonotaxis in these females. The potential effects of male exposure on the response of prothoracic auditory interneurons such as L3 are unknown. It had been reported that the L3 auditory interneuron in young virgin females exhibited decrementing response (reduction in the number of action potentials to consecutive sound pulses within a chirp) which has been interpreted as the major driver of syllable-period selective phonotaxis. L3s in old virgin females exhibit significant reduction in their decrementing response. Preliminary results suggest that regardless of age and in contrast to previous finding, L3s of male-exposed females fail to decrement in response to auditory stimuli, irrespective of syllable period. The implications of these results are discussed.

**Disclosures: B.A. Navia:** None. **C.R. Kent:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.11/KK28

**Topic:** F.01. Neuroethology

**Support:** NSF IOS 0917918

**Title:** Sex differences in sensorimotor coding for the production of duets in plain-tailed wrens

**Authors: *M. J. COLEMAN**[1], N. F. DAY[2], P. RIVERA-PARRA[3], E. S. FORTUNE[4]
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**Abstract:** Males and females routinely coordinate behaviors, especially in the context of mate selection and reproduction. This coordination requires that each individual integrate sensory cues from its partner to modulate its own motor programs. Plain-tailed wrens (Pheugopedius euophrys) produce a cooperative duet in which male and female birds rapidly alternate syllable production. This duet, which is used in territorial defence and pair bonding, can be coordinated using acoustic cues alone. We investigated the role of acoustic cues in the modulation of brain

activity in male and female wrens. We focused on the brain area called HVC as it is a premotor area necessary for song production that also receives acoustic information. In chronic neurophysiological recordings made in awake, behaving birds, there is little evidence of sensory responses in HVC activity in both males and females. Rather, activity appears to be pre-motor, with bursts of firing starting prior and continuing through the production of autogenous syllables. Nevertheless, there is evidence for sensory modulation of the motor program, as changes in the behavior of one bird are reflected in changes in HVC activity in the other bird during the duet. Interestingly, we observed 'motor replay' in awake birds of both sexes in the absence of syllable production. To further characterize the acoustic inputs to HVC, we replayed duet songs that were produced by the pairs during during these chronic neurophysiological experiments in subsequent acute experiments in which the birds were anesthetized with urethane. In the acute experiments, therefore, HVC activity is 'sensory-only' -- the animal hears its own vocal output and the vocal output of its partner. In this way, we were able to compare the activity in HVC in the context of singing (chronic experiment) and in relation to sensory coding (acute experiment). We found that changes in the activity in male HVC between chronic and acute recordings were more dramatic than in females. In females, we saw an expected shift in the timing of activity between chronic and acute recordings. Surprisingly, neural activity in males shifted dramatically between awake and anesthetized states. In awake birds, activity was characteristically premotor, occurring prior to and during male syllables. However, in anesthetized males, neurons responded strongly to female syllables and had very little response to male syllables. These data likely reflect distinct sex differences in the roles of each bird in the coordination and control of this cooperative behavior.

**Disclosures:** **M.J. Coleman:** None. **N.F. Day:** None. **P. Rivera-Parra:** None. **E.S. Fortune:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.12/KK29

**Topic:** F.01. Neuroethology

**Support:** University of Pennsylvania Research Foundation

University of Pennsylvania Center for Undergraduate Research and Fellowships

**Title:** State-dependency of viscerosensory input to the song motor system of passerine songbirds

**Authors: *J. BURKE**[1], J. MCLEAN[1], A. PERKES[2], M. F. SCHMIDT[1]
[2]Biol., [1]Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Motor performance is evaluated continuously by specialized brain circuits and used adaptively to modify behavior moment-to-moment as well as over longer time periods. During vocal behaviors, motor performance is evaluated by auditory feedback and likely also by sensory feedback from the vocal-respiratory periphery (defined henceforth as viscerosensory). Although much work has been performed on auditory feedback, little is known about how and where viscerosensory feedback is evaluated. In the avian song circuit, premotor nucleus HVC responds robustly to auditory stimuli but it is not known whether it also responds to viscerosensory stimulation. Sensory information from stretch receptors in the respiratory apparatus project through the vagus nerve to the nucleus of the tractus solitarius (nTS) up to PAm and eventually to HVC via intermediary thalamic nucleus Uva. Response in HVC to viserosensory stimulation would strengthen the hypothesis that viscerosensory feedback can have a direct influence on forebrain song control circuits.
Our preliminary findings investigating viscerosensory responses in HVC have been inconsistent. Delivery of brief air puffs through a cannula in the posterior air sac of anesthetized (Ketamine/Xylazine) adult male zebra finches elicited responses in less than 20% of recorded sites. We hypothesized that this inconsistency was caused, in part, by anesthesia-dependent suppression of sensory responses in the respiratory brainstem. We therefore performed new experiments in head-restrained awake birds. Under these conditions, we observed sensory responses in HVC but only when birds were quiet; brief arousal, often occurring upon delivery of multiple air puffs, caused suppression of responses. To prevent such arousal, we modified our experimental paradigm to record from HVC in head-restrained birds that were lightly sedated with diazepam. Under these conditions, our preliminary data suggest that neurons in HVC consistently show responses to brief air puffs delivered to the air sacs. We recorded extracellularly from 11 sites in 3 birds and found significant responses at each site with response latencies that ranged from 30 to 50 ms. To make sure that responses were specific to activation of receptors in the air sacs and not caused by click sounds associated with puff delivery, we placed the picospritzer in a sound-proof chamber and interleaved each experiment with controls to ensure that responses were not caused by auditory artifact. These preliminary results provide evidence for state-dependent viscerosensory responses in HVC. Future experiments will probe for response properties in PAm and Uva as well as in HVC of singing birds.

**Disclosures:** **J. Burke:** None. **J. McLean:** None. **A. Perkes:** None. **M.F. Schmidt:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.13/KK30

**Topic:** F.01. Neuroethology

**Support:** University of Pennsylvania Research Foundation

**Title:** Combining auditory and viscerosensory feedback perturbations in adult male zebra finches causes rapid song destabilization without recovery

**Authors: *K. M. MILLER**[1], C. S. LY[1], M. F. SCHMIDT[2]
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**Abstract:** The avian song system is an established model for studying learned vocal behavior. Juvenile songbirds crystallize their song using auditory feedback, which remains necessary for maintenance of adult stereotyped song. Disruption of auditory feedback by deafening causes song to deteriorate over a time period that varies across age and species. Because changes in song pattern are not evident until after the bird has produced many hundreds or thousands of songs, deafening-induced song degradation likely is caused by a slow accumulation of error. Viscerosensory feedback includes feedback from vocal musculature, air sacs, and lungs, and it is hypothesized to also play an important role in song maintenance. Song degradation caused by unilateral transections of the vagus nerve, which carries sensory information from the vocal-respiratory periphery, has been surprisingly modest. Typically, unilateral vagotomy causes immediate, but rather subtle, acoustic and temporal degradations of song which often show partial or full recovery within three days. This short time scale can be contrasted with the slower cummulative effect of deafening.
We hypothesized that if both types of feedback are necessary for song maintenance in a basal ganglia-dependent manner, then combining deafening with unilateral vagotomy should result in an increase in error accumulation and, as a consequence, a more profound and rapid degradation of song. Preliminary findings show effects not seen in deafening or vagotomy alone. We observe immediate acoustic deficits similar to previous studies following unilateral vagotomy, however, birds also show rapid acoustic and temporal song degradation that does not recover. Most significantly, we observe syllable omissions and significant variability in syllable duration within 1-2 weeks after nerve transection in deafened birds. Our findings suggest that perturbing both sensory feedback systems causes an accumulation of error that is greater than for each perturbation alone. Future experiments will investigate the role of the basal ganglia circuit in the context of this dual feedback perturbation paradigm.

**Disclosures: K.M. Miller:** None. **C.S. Ly:** None. **M.F. Schmidt:** None.

**Poster**

**503. Neuroethology: Social Behaviors**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 503.14/KK31

**Topic:** F.01. Neuroethology

**Support:** Chinese Ministry of Science and Technology grant 2015CB559201

**Title:** Neural activities during sexually dimorphic social behaviors

**Authors: *S. WANG**
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**Abstract:** C-fos studies indicate that the medial preoptic nucleus of the hypothalamus (MPOA) is activated during male sexual behavior and maternal care. However, to date little is known about the real-time dynamics of MPOA neural activities during behavior. In this study, we used fiber photometry to record MPOA calcium signal in freely moving male and female mice. We found that MPOA was strongly activated by socially relevant cues in both sexes. These results provide new insight into the neural mechanism through which MPOA regulates sexually dimorphic display of male sexual behavior.

**Disclosures: S. Wang:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.01/KK32

**Topic:** F.04. Stress and the Brain

**Support:** Start up funds awarded to Dr. Susanne Brummelte

**Title:** Acute and long-term biobehavioral outcomes following reduced maternal care and neonatal pain

**Authors: *S. M. MOONEY-LEBER**[1], J. YOUNG[1], S. BRUMMELTE[2]
[2]Dept. of Psychology, [1]Wayne State Univ., Detroit, MI

**Abstract:** Preterm infants are exposed to a multitude of painful procedures while in the neonatal intensive care unit. Although these procedures are in place to promote the survival of the infants, recent research suggests that exposure to many painful procedures may result in impaired brain development. In addition to pain, preterm infants also experience reduced maternal care with traditional incubator care. Preclinical models have indicated that reduced maternal care during the neonatal period results in impaired biobehavioral development. Thus, the current study sought to investigate the biological and behavioral consequences of neonatal pain in combination with reduced maternal care using a rodent model. Rat pups within a litter were assigned to one of 5 groups: unhandled control, tactile control, pain, reduced maternal care, and pain and reduced maternal care. Painful procedures consisted of needle insertion into alternating paws several times a day. Pups in the reduced maternal care groups were placed in a tea-ball infuser for 30 minutes immediately following administration of painful procedures or tactile stimulation. Two cohorts were used to analyzed the acute biological outcomes and the long-term behavioral

outcomes. The first cohort was sacrificed on postnatal day (PD) 4 and serum and brains were collected for enzyme-linked immunosorbent corticosterone assay and magnetic resonance spectroscopy. The second cohort was allowed to mature to adulthood and underwent cognitive and stress reactivity testing (starting on PD 79). Pups that experienced pain and/or reduced maternal care had significantly lower body weights on PD4. Further, exposure to reduced maternal care produced an increase in serum corticosterone and a reduction hippocampal glutamate/creatine ratio, whereas exposure to pain produced a reduction glutamate/creatine ratio in the frontal cortex. From these results, it is hypothesized that exposure to reduced maternal care and/or neonatal pain will produce impaired cognitive functioning and altered stress reactivity in adulthood. Our data suggests that neonatal pain exposure and/or reduced maternal care influence the hypothalamic-pituitary-adrenal axis and the glutamate/creatine ratio in regionally specific fashion, which in turn may influence biobehavioral outcomes later in life.

**Disclosures: S.M. Mooney-Leber:** None. **J. Young:** None. **S. Brummelte:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.02/KK33

**Topic:** F.04. Stress and the Brain

**Support:** R01MH100078-01A1

R01MH100078-03S1

**Title:** Early life stress alters amygdala-prefrontal cortex and amygdala-hippocampal connectivity in adult mice

**Authors: *F. K. JOHNSON**[1], J.-C. DELPECHE[1], G. J. THOMPSON[2], L. WEI[1], J. HAO[1], F. HYDER[2], A. KAFFMAN[1]
[1]Dept. of Psychiatry, Yale Med. Sch., New Haven, CT; [2]Dept. of Radiology & Biomed. Imaging and Magnetic Resonance Res. Ctr., Yale Univ., New Haven, CT

**Abstract:** In developed countries, childhood abuse and neglect are the most common and preventable causes of abnormal brain development. Often, the result is altered brain function and connectivity that persists into adulthood and is associated with a wide range of psychiatric and medical conditions. Among the most robust findings associated with early life stress (ELS) is abnormal amygdala size, hyperactivation in response to threats, and abnormal connectivity to other brain regions including the hippocampus and the prefrontal cortex. In this study we investigated the effects of ELS on amygdala connectivity and anxiety-like behaviors in a novel rodent model of early life stress called Unpredictable Postnatal Stress (UPS). Here we show that

UPS causes increased anxiety-like behavior in male but not female mice. This increase in anxiety is present in juvenile males and persists into adulthood. Using resting state fMRI (rsfMRI) we found hyperconnectivity between the amygdala and the prefrontal cortex and the amygdala and the hippocampus (both dorsal and ventral regions). Moreover, increased connectivity between the amygdala and these brain regions correlated with increased anxiety-like behavior. This study is the first to use rsfMRI to characterize amygdala connectivity in a mouse model of ELS and its findings are consistent with similar studies in maltreated children.

**Disclosures: F.K. Johnson:** None. **J. Delpeche:** None. **G.J. Thompson:** None. **L. Wei:** None. **J. Hao:** None. **F. Hyder:** None. **A. Kaffman:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.03/KK34

**Topic:** F.04. Stress and the Brain

**Support:** NIMH Grant 5R21MH097182

**Title:** Alterations in developmental microglia morphology and pro-inflammatory cytokine release resulting from early life stress and lipopolysaccharide injection in rats

**Authors: *K. R. GILDAWIE**, S. A. GOFF, J. R. ROWE-HILL, J. A. HONEYCUTT, P. GANGULY, V. THOMPSON, H. C. BRENHOUSE
Psychology, Northeastern Univ., Boston, MA

**Abstract:** Overwhelming evidence suggests that adversity during early life markedly increases vulnerability to a myriad of neuropsychiatric disorders including depression, anxiety, and schizophrenia. Importantly, stress during this time modifies circulating levels of stress hormones, which in turn has downstream effects on neuroimmune function. We hypothesize that these changes likely negatively impact overall neural development via neuroimmune signaling - particularly within the prefrontal cortex (PFC) - thereby leading to altered pathology associated with neuropsychiatric dysfunction. While the etiological mechanisms are not fully understood, resident microglia are thought to be a common source of increased neuroimmune activity through production of inflammatory molecules (e.g. cytokines, chemokines) in response to disruption in homeostasis. Microglia are capable of provoking long-term changes in brain structure and function, particularly within local microcircuitry. Importantly, they have the ability to become chronically sensitized, or ‘primed.’ to over-activation following insult. Early life stress (ELS) via maternal separation (MS) is thought to alter microglial reactivity to subsequent immune activation across development. In order to better understand the impact of MS on microglial priming in the developing immune system, rat pups were separated from their dams

for 4 hours per day from P2-20. In order to stress immune reactivity following MS, rats were exposed to the endotoxin lipopolysaccharide (LPS) at distinct developmental time points (P9, P20, or P40), and the concentrations of ramified and amoeboid PFC microglia were quantified to gain insight to activity states. Additionally, in order to assess the level of release of pro-inflammatory cytokines, quantitative RT-PCR was conducted on isolated microglia, allowing for the analysis of transcripts encoding only microglia-associated molecules, such as TNF-α and IL-10 throughout development. With this method, we are able to directly analyze the variations in neuroinflammatory changes at these distinct time points with ELS and LPS induced stress, providing compelling evidence for a role of early life adversity in altering microglia function in later life.

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**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.04/KK35

**Topic:** F.04. Stress and the Brain

**Title:** ELS is associated with precocious amygdala development and an unexpected dip in threat-associated freezing

**Authors: *K. G. BATH**[1], A. JOHNSEN[1], M. BRAVO[2], H. SHIN[3], G. MANZANO-NIEVES[4]
[1]CLPS, [2]Neurosci., Brown Univ., Providence, RI; [3]Brown University, Neurosci., Providence, RI; [4]Dept. of Neuroscience, Brown Univ., Providence, RI

**Abstract:** Early life stress (ELS) is associated with an increased risk for later development of emotional pathology such as depression and anxiety. The origins of pathology are thought to be rooted in atypical development of circuits regulating emotional responding, including the amygdala. Here we used a mouse model of ELS, in the form of maternal bedding restriction, and tested the effect on amygdala development, and the development of freezing behavior in a tone-associated fear conditioning paradigm. Previous work has established that tone-associated freezing develops as early 15 days of age and stays relatively stable across early development. Here, we found that mice reared under ELS conditions show an unexpected and significant dip in freezing behavior at 21 days of age. This dip in freezing behavior was associated with a precocious maturation and spike in the density and activity of Parvalbumin (PV)-positive cells in the basal amygdala (BA) . To test if the spike in PV-cells was related to suppressed freezing behavior, we took advantage of optogenetic techniques to silence this population of cells in the BA during acquisition and testing phase in the conditioning paradigm. We found that silencing BA PV cell restored normal levels of freezing behavior in ELS reared mice. These results have

implications for understanding the effects of ELS on the ontogeny of circuit development and its impact on the development and expression of fear associated responding.

**Disclosures: K.G. Bath:** None. **A. Johnsen:** None. **M. Bravo:** None. **H. Shin:** None. **G. Manzano-Nieves:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.05/KK36

**Topic:** F.04. Stress and the Brain

**Support:** Norman Prince Neuroscience Institute New Frontiers Award

Brown Institute for Brain Sciences

Hassenfeld Child Health Innovation Award

**Title:** Early life stress: In depth analysis of maternal behavior in response to limited access to bedding

**Authors: *M. E. GALLO**[1], T. CAMPBELL[2], A. OLANIYAN[1], C. E. LOPEZ[1], K. G. BATH[1]
[1]Cognitive, Linguistic and Psychological Sci., [2]Neurosci., Brown Univ., Providence, RI

**Abstract:** Early life adversity increases the lifetime risk for pathology and profoundly impacts neural development. Multiple mouse models of early life stress (ELS) have been developed to aid in understanding the mechanisms underlying risk for pathology development. In recent years, a limited bedding (LB) paradigm has been developed, in which early life stress is induced by limiting dams' access to bedding and nesting resources during defined periods of pup development (Rice et al., 2008). In the current study, we use 24/7 video monitoring to more thoroughly characterization LB manipulation effects on maternal behavior over the circadian cycle, as well as the evolution of changes in maternal behavior across the duration of the ELS paradigm. We also assess maternal behavior prior to and following the completion of the ELS manipulation. Maternal behaviors, including nesting, eating, drinking, and walking, were characterized using a combination of Ethovision automated tracking and hand scoring of videos over the circadian cycle. We have previously characterized the effects of LB manipulations on measures of cognitive, affective, and neural development. As an initial pilot study, we will also provide data related the impact of LB manipulations on development and ELS-associated effects on immune activation in peripheral blood mononuclear cells and neural tissue.

**Disclosures:** **M.E. Gallo:** A. Employment/Salary (full or part-time):; Brown University. **T. Campbell:** None. **A. Olaniyan:** None. **C.E. Lopez:** A. Employment/Salary (full or part-time):; Brown University. **K.G. Bath:** A. Employment/Salary (full or part-time):; Brown University.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.06/LL1

**Topic:** F.04. Stress and the Brain

**Support:** Norman Prince Neuroscience Institute

New Frontiers Award

Brown Institute for Brain Sciences

Hassenfeld Child Health Innovation Award

NSF GRFP to GMN

**Title:** Brain-derived neurotrophic factor: A potential driver of the accelerated neurobehavioral development induced by early-life stress

**Authors: *G. MANZANO-NIEVES**[1], K. B. HUNTZICKER[2], K. H. HAJDAROVIC[2], K. G. BATH[3]
[1]Dept. of Neuroscience, Brown Univ., Providence, RI; [2]Neurosci., [3]CLPS, Brown Univ., Providence, RI

**Abstract:** In humans, childhood exposure to abuse leads to an elevated risk for the development of psychopathology in adulthood. Although much research has investigated the long-term implications of early-life stress (ELS) in adults, its effects on development and the mechanisms it employs remain largely unknown. Here we used a form of ELS to study the underlying mechanisms through which ELS alters neuronal development impacting contextual fear memory expression. Our ELS paradigm restricted maternal access to bedding and nesting materials from postnatal days (P) 4 to 11. Previous data from our lab demonstrates that this form of ELS accelerates the emergence of adolescence-associated fear suppression from P28 to P21. To uncover the underlying mechanism, we obtained hippocampal samples of control and ELS animals at multiple developmental time points (P4 through adulthood). mRNA quantification of brain-derived neurotrophic factor (BDNF) and truncated track b receptor (TrkB.T1; an endogenous dominant negative receptor for BDNF) mRNA revealed a significant increase in BDNF mRNA at P12 accompanied by a decrease in TrkB.T1 mRNA. These results suggest that ELS may lead to a robust increase in BDNF availability at P12. Furthermore, the proliferation of

parvalbumin positive neurons (PV+), known to be a BDNF-initiated process, was revealed by immunohistochemical analysis to be increased in ELS animals at P21 when compared to controls. This acceleration of generation PV+ neurons led us to hypothesize that ELS serves to elevate BDNF and drives the acceleration seen in limbic system development. To test this hypothesis, we employed a genetic approach in which we attempt to both negate the effects of ELS by reducing the amount of functional BDNF via both a Val66Met mutation and BDNF knockout, and to phenocopy the behavioral effects of ELS by genetically eliminating the TrkB.T1 receptor. Our preliminary results suggest that animals which have undergone ELS but have decreased secretion of mature BDNF lack the suppression of fear expression normally observed in wild-type ELS mice at P21.

**Disclosures: G. Manzano-Nieves:** None. **K.B. Huntzicker:** None. **K.H. Hajdarovic:** None. **K.G. Bath:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.07/LL2

**Topic:** F.04. Stress and the Brain

**Support:** NIH F31 MH111131 NRSA

Norman Prince Neuroscience Institute New Frontiers Award

**Title:** Sex-selective effects of early life stress on the development of attentional deficits

**Authors: *H. GOODWILL**, S. LIN, E. OYERINDE, K. BATH
Brown Univ., Providence, RI

**Abstract:** Stress incurred early in life influences emotional development and increases the lifetime risk for and severity of affective pathology. Women have a heightened susceptibility to the effects of early life stress (ELS) and are twice as likely than men to develop stress-associated pathology, such as depression. Depressive pathology is highly co-morbid with cognitive impairments and inflexibility, resulting predominantly from frontal lobe dysfunction. The prefrontal cortex (PFC), which orchestrates the integration of cognition and emotion through cortical and subcortical pathways, is especially sensitive to chronic and early life stress. We recently demonstrated that female mice exposed to ELS, in the form of maternal bedding restriction, show a sex-selective development of depressive-like behavior and are more severely impaired than male and control mice in rule-reversal learning ($p<0.01$) during an attentional set shifting task. Using optogenetic inhibition of fast spiking (FS) GABAergic interneurons containing the calcium binding protein parvalbumin (PV) in the orbitofrontal cortex (OFC)

of control animals, we can phenocopy the deficits observed in ELS-exposed females. In the OFC, ELS was also associated with a decrease in PV mRNA levels ($p<0.05$), and a female specific decrease in GAD67 ($P<0.01$), a GABA synthesizing enzyme. Here we investigate the developmental time-course of these impairments and the potential underlying mechanisms by which ELS alters PV interneuron development in this region. This work addresses the mechanisms supporting sex differences in risk for the development of affective pathology, which is a relevant and largely overlooked public health concern. It lays the foundation for predictions regarding risk factors and biomarkers that underlie sex differences in vulnerability to stress and associated cognitive impairments linked with depression.

**Disclosures: H. Goodwill:** None. **S. Lin:** None. **E. Oyerinde:** None. **K. Bath:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.08/LL3

**Topic:** F.04. Stress and the Brain

**Title:** Transgenerational effects of *In utero* stress on spontaneous behavior and glutamate receptor expression in *Caenorhabditis elegans*

**Authors: K. J. HUGHES**[1], A. D. MEUSER[1], L. E. BEANE[1], E. R. TAYLOR[2], Z. ZHU[3], *J. K. ROSE[2]
[1]Behavioral Neurosci. Program, [2]Psychology, Western Washington Univ., Bellingham, WA; [3]Sch. of Life Sci., Northwest Univ., Xi'an, China

**Abstract:** Previous studies in rodents have reported that prenatal stress can result in adult progeny that show decreased neuronal volume and glutamate receptor expression in the hippocampus, as well as decreased spatial memory performance, and increased anxiety- and depression-like behaviors in open field or forced swim tasks. Studies have also reported that maternal stress during pregnancy can lead to increased expression of specific DNA methyl transferases suggesting epigenetic alterations in gene expression in offspring. In *Caenorhabditis elegans*, extreme heat stress has been shown to decrease adult fecundity while exposure to less severe stressors during worm development increases resistance to oxidative stress in later generations via epigenetic mechanisms. To examine the potential transgenerational effects of in utero stress in *C. elegans*, adult worms were exposed to a mild stressor for ~4 hours; a duration that corresponds to egg formation. Worms were then either bleached for egg collection or were observed for spontaneous behaviors by measuring frequency of reversals and behavioral variability. Spontaneous behaviors were also then measured for subsequent F1 and F2 generations. Preliminary results indicate a decrease in spontaneous reversals in adult progeny of stressed animals compared to progeny of worms exposed to sham or control conditions. Research

in rodents suggests that prenatal stress modulates glutamate signaling in offspring, typically via downregulation of glutamate receptors. To study this possibility in *C. elegans* across generations, expression of *glr-1* (non-NMDA type glutamate receptor) was measured using qRT-PCR. As well, patterns of expression and regulation of GLR-1 receptors were assessed in vivo with confocal imaging of GLR-1::GFP. Taken together, this work could help elucidate the broad effects of in utero stress and provides additional support for the use of the *C. elegans* model system to investigate transgenerational effects of parental experience.

**Disclosures: K.J. Hughes:** None. **A.D. Meuser:** None. **L.E. Beane:** None. **E.R. Taylor:** None. **Z. Zhu:** None. **J.K. Rose:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.09/LL4

**Topic:** F.04. Stress and the Brain

**Support:** NICHD 1R01HD087509-01

NIGMS 1P20GM103653

**Title:** Rescue of sex-specific phenotypic outcomes of exposure to early-life stress using pharmacological interventions

**Authors: *S. M. KELLER**, T. S. DOHERTY, A. NOWAK, T. L. ROTH
Univ. of Delaware, Newark, DE

**Abstract:** Experiencing maltreatment by the caregiver can have lifelong consequences for the brain and behavioral trajectories. Epigenetic mechanisms are one potential way via which early-life experiences are capable of inducing long-term effects. In the current study, rodents were exposed to brief bouts (i.e. 30 minutes per day) of caregiver maltreatment for the first seven days of life. Previous work employing this model has shown that adult females exposed to this perturbation during infancy maltreat their own offspring, show altered behavior in the forced swim test, and exhibit alterations in epigenetic marks such as DNA methylation throughout the brain. Because changes in phenotypic outcomes associated with experiencing maltreatment are sex-specific, we conducted one study to examine sex differences in infant caregiving during our maltreatment paradigm. Data indicate that more adverse maternal behaviors are performed toward female, as compared to male, pups in our model of caregiver maltreatment. As the role of epigenetic alterations in causing phenotypic outcomes resulting from caregiver maltreatment is unclear, we conducted a second study where we administered zebularine, a drug which inhibits DNA methylation, to adult female rats. Maternal behavior and behavior in the forced swim test

were measured after a week of zebularine administration. Data indicate zebularine administration normalizes behavior and DNA methylation aberrations associated with maltreatment. Changes in gene expression following our pharmacological intervention will also be presented.

**Disclosures: S.M. Keller:** None. **T.S. Doherty:** None. **A. Nowak:** None. **T.L. Roth:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.10/LL5

**Topic:** F.04. Stress and the Brain

**Support:** NIGMS 1P20GM103653

NICHD 1R01HD087509-01

**Title:** An investigation into pharmacological prevention of epigenetic traces left by early-life stress

**Authors: *T. S. DOHERTY**, J. R. CHAJES, T. L. ROTH
Univ. of Delaware, Newark, DE

**Abstract:** Early life stress, particularly within the caregiving relationship, is a major precipitating factor for psychiatric and cognitive disorder. While the mechanisms underlying this connection have yet to be elucidated, epigenetic alterations are leading candidates. We have previously reported altered patterns of methylation associated with exon IX of the brain derived neurotrophic factor (*Bdnf*) gene in the prefrontal cortex of rats following exposure to caregiver maltreatment. Given that *Bdnf* is critical to developmental processes and that its dysregulation is heavily implicated in altered cognitive function and in several psychiatric disorders, aberrant methylation of this gene may underlie altered behavioral trajectories associated with early-life stress. Thus, the aim of this work was to assess the ability of epigenetic drugs (i.e. those that inhibit critical epigenetic enzymes) to prevent altered patterns of methylation at *Bdnf* exon IX previously discovered in our maltreated rats. Infant male and female Long Evans rats were subjected to either nurturing care (from their biological mother or a foster dam) or maltreatment from a foster dam for 30 minutes daily from postnatal days (PN) 1 to 7. One of three drugs (inhibiting either HDACs or DNMTs) or an appropriate vehicle was administered daily to each group prior to caregiving manipulations. Brains and plasma were extracted 24 hours after the last manipulation (on PN8) for methylation analysis. Data demonstrate that both HDAC and DNMT inhibition prevent methylation alterations associated with caregiver maltreatment. Results will be discussed in the framework of epigenetic mechanisms and interventions in early-life stress.

Future work will focus on the utility of epigenome modifiers to prevent aberrant behavioral outcomes associated with maltreatment.

**Disclosures: T.S. Doherty:** None. **J.R. Chajes:** None. **T.L. Roth:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.11/LL6

**Topic:** F.04. Stress and the Brain

**Support:** NIH Grant MH078105

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**Title:** Effects of adverse maternal care on the development of hypothalamic-pituitary-adrenal axis function in nonhuman primates

**Authors: *S. N. BRAMLETT**[1,2], E. L. MORIN[1,2], D. B. GUZMAN[2,1], B. R. HOWELL[3,1,2], J. S. MEYER[4], M. SANCHEZ[1,2]
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**Abstract:** Early life stress (ELS) is a known risk factor for psychopathology, including anxiety and depressive disorders, substance abuse, as well as cognitive and behavioral deficits. The mechanisms underlying this association, however, remain poorly understood. A likely biological link between ELS and many psychopathologies is its impact on typical development of the hypothalamic-pituitary-adrenal (HPA) axis. Studying this relationship in humans can be challenging due to limitations in prospective studies, as well as confounding factors, such as co-morbid conditions and genetics. To circumvent these difficulties, our group used a translational and well-established ELS model of infant maltreatment by the mother in rhesus macaques. This ELS model consists of comorbid infant abuse and rejection by the mother during the first months of life. To disentangle the effects of the adverse experience from those due heritable factors, infant macaques (n=43) were cross-fostered at birth and randomly assigned to either control (n=21) or maltreating (MALT; n=22) foster mothers. We assessed the developmental impact of adverse care on HPA axis function longitudinally since birth through the juvenile period using (1) measures of hair cortisol (CORT) accumulation, (2) diurnal CORT rhythm, and (3)

glucocorticoid negative feedback via dexamethasone (DEX) suppression tests. Our findings indicate that, although hair CORT levels were not different at birth, MALT infants showed significantly higher CORT accumulation than controls from birth through 6 months, with a parallel trend towards elevated plasma CORT levels. Long-term impact of adverse caregiving was detected at 12 months, with a significant interaction effect between MALT and sex on diurnal CORT rhythm, with MALT females exhibiting higher CORT levels at both the morning and afternoon time points than control females. This effect was not observed in the males. MALT subjects of both sexes showed super-suppression of CORT secretion in response to DEX challenge at 12 months. Neither of the diurnal or DEX suppression effects observed at 12 months were present at 18 months. These data suggest that alterations in HPA function due to maternal maltreatment persist past the early infant period of ELS exposure into the early juvenile period, but are ultimately temporary. Additionally, females are more sensitive to maltreatment-related HPA dysregulation than males. Although HPA axis activity seems to start to recover later in the juvenile period, chronic exposure to high levels of CORT during the first 12 months of life are expected to have long-term consequences for brain, physiological and behavioral development.

**Disclosures: S.N. Bramlett:** None. **E.L. Morin:** None. **D.B. Guzman:** None. **B.R. Howell:** None. **J.S. Meyer:** None. **M. Sanchez:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.12/LL7

**Topic:** F.04. Stress and the Brain

**Title:** Biochemical and behavioral effects of environmental enrichment on strain-dependent vulnerability to anxiety and depression in the chick separation stress paradigm

**Authors: *M. K. JOURDAN**[1], S. M. ANCHOR[1], S. W. WHITE[1], P. K. SHARMA[2], S. MURTHY[2], K. J. SUFKA[1]
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**Abstract:** Increased attention has been directed towards determining how environment interacts with genetics on the manifestation of stress-related disorders. This study investigates the differential effects of an enriched versus impoverished environment on behavioral and biochemical endpoints of depression between stress-vulnerable and stress-resilient strains in the chick anxiety-depression model. Black Australorp and Production Red strains were housed in either enriched or impoverished conditions for 4 days followed by a 90 min social isolation test. Rate of distress vocalizations (DVocs) were recorded throughout the isolation period and latency to behavioral despair was calculated. Immediately following testing, bilateral hippocampal tissue

was harvested and brain-derived neurotrophic factor (BDNF) levels were analyzed via an ELISA assay. Regardless of housing conditions, stress-vulnerable Black Australorps entered behavioral despair more quickly than the Production Reds. Significant decreases in BDNF were seen as a result of an isolation stressor, but were dependent on the complex interaction of genetic line and housing stress conditions. Decreases in BDNF were only detected in Black Australorps housed in impoverished conditions and the Production Red housed in enriched conditions. These findings may be relevant to understanding the importance of an individual's environment when treating anxiety and depression in stress-vulnerable populations.

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**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.13/LL8

**Topic:** F.04. Stress and the Brain

**Support:** CIHR grant 114885

**Title:** Limited bedding conditions during a first lactation episode induces morphological plasticity in the prefrontal cortex and increases attentional flexibility in early lactating multiparous female rats

**Authors: *C.-D. WALKER**[1,3], E. A. OPALA[3], S. VERLEZZA[3], H. LONG[3], D. RUSU[2], B. WOODSIDE, H4A 2Z7[4]
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**Abstract:** Multiparous (M) females are known to display a significant increase in dendritic spines in the amygdala, septum and hippocampal CA1 compared to primiparous (P) and virgin (V) females, but regions important for cognitive processing, attention and modulation of sequential behaviors such as the medial prefrontal cortex (mPFC) have not been thoroughly investigated. Because of the critical role of the mPFC in "gating" stress and emotional responses, and in modulating some aspects of maternal behavior, a history of stress during a first lactation episode might significantly alter morphological and functional plasticity in this structure in subsequent lactation periods. We compared neuron morphology in mPFC between primiparous and multiparous lactating female rats on postpartum day, PPD5 that had been exposed to the chronic stress of limited bedding and nesting material (LB) during PPD1-10 of a first lactation or that had normal bedding (NB). Golgi-Cox stained neurons in layer II/II of prelimbic (PL) or

infralimbic (IL) mPFC were analyzed. We also examined whether enduring effects of the LB could be observed on attention capabilities in multiparous females, using the attention set shifting task (AST) in PPD5 females. Compared to virgins, all parous female groups exhibited increased spines and dendritic length in the IL, but not the PL mPFC. In the PL, dendritic length was reduced in multiparous females compared to P or V rats. Sholl analysis of the IL neurons revealed that total spines were higher in LB groups than control NB groups, whether they were multiparous and nursing (M) or parous and 2 weeks post weaning (NL). In contrast, P females exposed to adverse LB conditions exhibited a significant reduction in total spines, dendritic length and spine density compared to controls, demonstrating an acute negative effect of LB on IL mPFC morphological plasticity. When tested for attentional capabilities, LB multiparous females on PPD3 showed the lowest number of trials to completion and total errors in the extradimensional shift, a measure of attention mostly linked to mPFC activity. Overall these results suggest that exposure to adverse environmental conditions while nursing significantly affects neuronal morphology in the IL mPFC of mothers and causes both an acute reduction and long-term compensatory increase in spines in this region that persists in multiparous females. These morphological changes associate with greater attentional flexibility, a behavioral change that might be adaptive to the care of the young under adverse conditions.

**Disclosures: C. Walker:** None. **E.A. Opala:** None. **S. Verlezza:** None. **H. Long:** None. **D. Rusu:** None. **B. Woodside:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

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**Title:** Effects of maternal separation on the serotonin system in the dorsal raphe nucleus of Tph2 deficient mice

**Authors: M. W. LIEB**[1], M. ARNOLD[2], K. T. NGUYEN[2], K. S. SCHNABEL[2], M. WEIDNER[4], J. WAIDER[5], *C. A. LOWRY[3], K.-P. LESCH[5]

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**Abstract:** Brain serotonergic systems have been implicated in cognitive control and emotion regulation. The rate-limiting enzyme for synthesis of serotonin in the brain is tryptophan hydroxylase 2 (Tph2). There is accumulating evidence that Tph2-deficient mice display disruptions in behavioral phenotypes relevant to stress-related psychiatric disorders, including trauma-, anxiety-, and affective disorders. Furthermore, early life stress, such as maternal separation, can influence *tph2* mRNA expression, as well as *tph2* mRNA expression responses to stress exposure, in adulthood. The aim of this study was to determine how maternal separation affects mRNA expression of serotonin-related genes in the doral raphe nucleus (DR), including *tph2*, the high affinity, low capacity, sodium-dependent serotonin transporter (*slc6a4*), the serotonin type 1a receptor (*htr1a*), the low affinity, high capacity sodium-independent serotonin transporter, organic cation transporter 3 (*slc22a3*), corticotropin-releasing hormone receptor 1 (*Crhr1*), and corticotropin-releasing hormone receptor 2 (*Crhr2*). Male wild type, homozygous and heterozygous *Tph2* knockout mice were exposed to either animal facility rearing control conditions or maternal separation, consisting of daily separation (3 h) of mixed sex litters from the dam from postnatal day 2 (P2) until P15. During separation, pups were maintained under red-light at 29 °C and humidity of 65-70%. On P25, pups were weaned and males were group housed in groups of 3-6. Mice were euthanized as adults on day P100-110. Maternal separation differentially altered serotonergic gene expression in wild type, homozygous and heterozygous Tph2 knockout mice in a topographically specific manner within the DR. The patterns of changes in gene expression were consistent with a previously described anxiety and panic-prone phenotype of homozygous and heterozygous *tph2* knockout mice. Overall, these data are consistent with the hypothesis that gene x environment (G x E) interactions, including serotonergic genes and adverse early life experience, play an important role in vulnerability to trauma-, anxiety-, and affective disorders during adulthood.

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**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.15/LL10

**Topic:** F.04. Stress and the Brain

**Support:** NSF IOS-1557451

GSU Brains and Behavior Seed Grant

**Title:** Effects of delaying parturition on patterns of cell death in the perinatal mouse brain

**Authors: *A. CASTILLO-RUIZ**, M. MOSLEY, N. G. FORGER
Neurosci. Inst., Georgia State Univ., Atlanta, GA

**Abstract:** Post-mitotic cell death is a key event in the development of the nervous system. Despite the established importance of this process, little is known about what initiates or terminates the cell death period. We previously reported striking changes in cell death across multiple regions in the mouse brain following birth, with some regions showing abrupt decreases (e.g., paraventricular nucleus of the hypothalamus (PVN)) and others increases (e.g., CA1 oriens layer of the hippocampus). These results suggest that birth (parturition) may trigger changes in cell death. Alternatively, the timing of cell death may be developmentally programmed and independent of birth. To distinguish between these competing hypotheses, we manipulated gestation length in C57BL/6 mice, a strain in which birth occurs on average at 19.3 days post-coitum (dpc). We established timed-pregnancies and injected dams subcutaneously with oil or with progesterone on 17 and 18 dpc. This progesterone treatment extends pregnancy by one day and mimics the hormonal profiles seen in dams that give birth "late." All animals were vaginally delivered at 19 dpc (controls) or 20 dpc (progesterone-treated). Male and female pups were weighed and euthanized on postnatal day (P) 0, 1 and 2, and their brains were collected for immunohistochemical detection of activated caspase 3, a marker of cell death. For both groups, increases in body weight were associated with birth (days *ex utero*) and not with dpc. In contrast, cell death patterns in the PVN and CA1 oriens layer were associated with dpc irrespective of *ex utero* age. This suggests that perinatal cell death patterns are developmentally programmed, whereas body growth depends on birth. Interestingly, our previous results in the PVN and CA1 oriens layer also show that birth mode (C-section vs vaginal) can alter perinatal cell death patterns, which hints that even though these patterns may be developmentally programmed under normal circumstances (vaginal birth), they can be influenced by experience/environment. Together our results contribute to the understanding of how developmental neuronal cell death is regulated.

**Disclosures: A. Castillo-Ruiz:** None. **M. Mosley:** None. **N.G. Forger:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** F.04. Stress and the Brain

**Support:** NSF-IOS-1557451

GSU Brains and Behavior Seed Grant

**Title:** Neural activation triggered by birth in the neonatal mouse brain

**Authors: *Y. C. DAVILA-VAZQUEZ**[1], A. CASTILLO-RUIZ[1], C. CHEVER[2], N. G. FORGER[1]
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**Abstract:** Birth is a dramatic event in the life of placental organisms, involving hormonal surges, uterine contractions and modifications in key peripheral organs. Parturition has been described as an "adaptive stressor" that prepares the fetus for life outside the womb, but how or if birth affects brain development is not well understood. We recently found marked changes in cell death shortly after birth in several brain regions. Furthermore, the pattern of cell death differed significantly between vaginally- and cesarean-delivered pups across multiple brain areas, suggesting an important role of birth mode in the patterning of cell death. The paraventricular nucleus of the hypothalamus (PVN) showed the largest effect of birth mode on cell death, with a transient ~3-fold increase ($P<0.01$) in the density of dying neurons in cesarean sectioned mice on the day of birth. These results suggest that the PVN is particularly sensitive to stimuli at birth. To test the hypothesis that birth triggers neural activation in the PVN, we established timed-pregnancies and collected the brains of male and female offspring *in-utero* at embryonic day (E) 18 (one day before expected delivery), and *ex-utero* at postnatal day (P) 0 (1h and 3h after birth) and P1. Brains were immunohistochemically stained for the expression of the immediate early gene, c-Fos, as a marker of neural activation. We find that the density of c-Fos immunoreactive (Fos-ir) cells in the PVN is about 300% higher on P0 (3h after birth) than on E18 ($p<0.0001$). Fos-ir cell density returned to baseline 24 hours later ($p<0.0001$ for P0 vs P1). A similar pattern was seen in the supraoptic nucleus of the hypothalamus, suprachiasmatic nucleus of the hypothalamus, paraventricular nucleus of the thalamus, subfornical organ, caudate putamen and the lateral habenula. Most brain regions that show Fos-ir cells contain vasopressin and/or oxytocin neurons or receive input from vasopressin and/or oxytocin neurons. We are currently performing fluorescent double-labeling to test the hypothesis that neural populations activated at birth co-localize oxytocin or vasopressin with c-Fos.

**Disclosures: Y.C. Davila-Vazquez:** None. **A. Castillo-Ruiz:** None. **C. Chever:** None. **N.G. Forger:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

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**Program#/Poster#:** 504.17/LL12

**Topic:** F.04. Stress and the Brain

**Support:** NSF IOS 11-18792

F31 ES026890-02

**Title:** Transgenerational effects of parental dim light at night on offspring immunity and behavior

**Authors: *Y. M. CISSE**[1], K. L. RUSSART[2], R. J. NELSON[2]
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**Abstract:** Environmental light is the most potent signal for synchronizing the circadian system. Disruption of natural light/dark cycles by light at night (LAN) dampens endogenous biological rhythms that maintain optimal function of various systems, including the endocrine, affective, and immune systems. Indeed, exposure to Dim LAN (dLAN) exposure (5 lux) impairs innate and cell mediated immune responses, and increases depressive-like behavior in a TNF-alpha dependent manner in Siberian hamsters (*Phodopus sungorus*). Because of potential transgenerational effects of dLAN, we hypothesized that parental exposure to dLAN *prior* to mating impairs offspring physiological and behavioral immune responses. Adult male and female Siberian hamsters were exposed to either dark nights (DARK) or dLAN for 8 weeks, then paired, mated, and thereafter housed in dark nights. Pairings resulted in four groups: DARK-DARK (Male-Female), DARK-dLAN, dLAN-DARK, and dLAN-dLAN. Separate subsets of adult offspring were tested for adaptive immune, innate immune, and affective responses. Maternal exposure to dLAN dampened cell-mediated immune responses in male and female offspring, increased IgG antibodies to a novel antigen, and decreased sucrose preference. Paternal exposure to dLAN reduced cell-mediated immune responses in female offspring and increased time spent floating in the Porsolt swim test. Melatonin and glucocorticoid receptor expression were altered in the spleen and hippocampus of offspring in a parental sex-specific manner. Global methylation in the spleen decreased in response to parental dLAN. Data will also be presented for febrile, anhedonic, locomotor, and cytokine responses to an endotoxin challenge. Altered immune and affective responses in offspring that have experienced dLAN in the germline indicates that seemingly innocuous nighttime lighting may have transgenerational health consequences.

**Disclosures:** **Y.M. Cisse:** None. **K.L. Russart:** None. **R.J. Nelson:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.18/LL13

**Topic:** F.04. Stress and the Brain

**Title:** Early life stress reduces neuropathic pain in adulthood - is alteration of spinal microglial reactivity critically involved?

**Authors: J. GENTY**[1], M. TETSI NOMIGNI[1], *P. J. HEUSCHLING[2], F. ANTON[1], U. HANESCH[1]
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**Abstract:** Growing evidence underlines the association between early life adversity and persistent alterations of neural, endocrine and immune functions that may be accompanied by a host of disease patterns such as chronic pain in later life. Neuropathy is a debilitating condition presenting a substantial co-occurrence with stress-related disorders. Despite the established overlapping of biochemical pathways involved in the etiology of these disorders, the intricacy of their mutual interdependence remains. In this context, immunocompetent cells are largely affected during chronic stress and are a key factor in the sensitization of nociceptive dorsal horn neurons. The goal of the present study was to investigate the impact of maternal separation (MS), a well-established model of early life stress in rodents, on chronic constriction injury (CCI)-induced neuropathic pain and to reveal the relevance of spinal microglia activation and pro-inflammatory cytokine regulation.
For this purpose 12 groups of rats were exposed to different combinations of stress condition, CCI-injury and pharmacological treatment. Noxious sensitivity was tested during baseline conditions as well as during subsequent neuropathic and pharmacological treatment conditions. Von Frey hair and the cold plate tests were used for the assessment of mechanical and cold hyperalgesia/allodynia. Amphotericin B, a substance known to activate monocytes and macrophages in the periphery and microglial cells in the CNS was administered to subgroups of animals. At the end of the protocol, rats were sacrificed to assess microglial activation using qPCR and immunohistochemistry.
Our main finding was that maternal separation led to a reduction of CCI-related pain hypersensitivity (thermal and mechanical hyperalgesia/allodynia). We concomitantly observed a downregulation of Iba 1, mRNA a marker of microglial cells, and of IL-1β mRNA, a pro-inflammatory cytokine that may be released by microglia. According to preliminary results, Amphotericin B in turn seemed to enhance CCI-related pain sensitivity, possibly via an activation of microglia.
Our results show that MS may lead to a reduction of neuropathy-related pain in adult age. Stress-related dampening of spinal microglial reactivity may play a critical role in this context.

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**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.19/LL14

**Topic:** F.04. Stress and the Brain

**Title:** The excitation-inhibition balance in prefrontal cortex neurons during development after early life stress: Influence of the mineralocorticoid receptor

**Authors: *H. KARST**[1], R. A. SARABDJITSINGH[1], M. JOELS[2]
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**Abstract:** The excitation-inhibition (EI) balance plays an important role during maturation of the brain. A disturbance of the balance may lead to the development of psychiatric disorders. Early life stress (ELS) can cause impairments in cognitive and a variety of behavioral functions later in life. It is hypothesized that a disturbance of the EI balance may underlie these abnormalities. In this study we followed the EI balance during maturation by recording the glutamatergic and GABAergic transmission from neurons in the infralimbic medial prefrontal cortex (imPFC). Mice were stressed from postnatal day (PND) 2 until PND9 using the limited nesting and bedding model. At PND9, PND21 (weaning), at 6 weeks (adolescent) and at 10-12 weeks (adult) male mice were used for ex vivo electrophysiology. In slices of the imPFC we recorded the evoked glutamate (AMPA) current in layer 2/3 cells at a holding potential of -65 mV. In the same neuron evoked GABA currents at +10mV and evoked NMDA currents at +50 mV were recorded. Beside the evoked currents, we also recorded the spontaneous miniature excitatory (mEPSCs) and inhibitory currents (mIPSCs). The mEPSCs were recorded at -65 mV and in the same neuron the mIPSCs were recorded at +10mV. To study the morphology of the neurons during maturation, we filled the neurons with biocytin, which was added to the pipette solution. After recoding, the slices were fixated in paraformaldehyde and later stained with an antibody for biocytin in combination with DAB. From previous studies we know that a high expression of the mineralocorticoid receptor (MR) alleviates the effects of ELS in mice or rats. In this study we investigated the effect of ELS in mice with a lower MR expression (heterozygous MRKO) compared to wildtypes. As was expected, we observed a tremendously high EI ratio at PND9. This, however, was not seen in ELS mice of that age. From adolescence onwards, ELS and control mice were comparable. Yet, the AMPA/NMDA ratio in the adult mice was lower in ELS compared to wildtype mice. In heterozygous MRKO mice the effect of ELS on the AMPA/NMDA ratio seems to appear at an earlier age. ELS furthermore decreased dendritic complexity and the length of apical and basal dendrites of pyramidal neurons in the imPFC in adult male mice, while no effects were seen in adolescent mice. MRKO amplified the effects of ELS on these neurons. We conclude that the EI balance in ELS mice is changed early in life,

followed by a change in the AMPA/NMDA ratio later in life and that a lower MR expression seems to accelerate the effect on the AMPA/NMDA ratio. The morphological changes appear to go hand in hand with the affected AMPA/NMDA ratio.

**Disclosures: H. Karst:** None. **R.A. Sarabdjitsingh:** None. **M. Joels:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

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**Title:** Shaping genetic resilience to early life stress: Sex-specific modulation of mineralocorticoid receptor function on neuroendocrine stress reactivity and behavior in mice

**Authors: *R. A. SARABDJITSINGH**[1], V. BONAPERSONA[1], H. MEEUSEN[1], R. DAMSTEEGT[1], K. SPARNAAIJ[1], R. DE KLOET[2], M. JOËLS[1,3]
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**Abstract:** Adverse environmental factors (such as early life stress (ELS)), in interaction with genetic predisposition, are considered major risk factors for the development and precipitation of psychopathology. Prevailing clinical and rodent studies have shown that the brain mineralocorticoid receptor (MR) may play a key role in shaping resilience to early life stress effects, especially in females. Yet, the mechanism explaining how MR can moderate the effects of ELS on brain function is still poorly understood.
Here we investigated whether i) chronic early life stress (limited nesting/bedding model postnatal day 2-9) affects acute stress reactivity, physiological and behavioral parameters relevant for mood disorders; ii) whether this is exacerbated in the forebrain-specific MR knockout (MRKO; Cre-LoxP system) mouse and iii) if these effects are sex-dependent.
We used a test battery that screens various behavioral domains across development from 4 weeks onwards. Experimental groups consisted of male and female MRKO or wildtype littermate control (flox) mice subjected to either control or ELS condition. For instance, in males, from 4 weeks onwards ELS increased anxiety-related behavior which persisted into adulthood. Anxiety was not affected in females. Results in other behavioral domains (i.e. social behavior and

memory) are currently being analyzed. Preliminary analyses suggest that the effects of ELS and/or MRKO are highly domain- and sex-specific suggesting that ELS affects the brain in a highly complex manner yet differently for specific functional circuits. Interestingly, acute stress reactivity was also sex-dependently regulated. In all experimental groups, restraint stress (10 min) effectively evoked a transient and acute stress response with peak corticosterone levels at approximately 20 min after onset. This stress response did not differ between the male groups (ELS, MRKO). In the females however, compared to controls, both ELS and MRKO resulted in blunted stress peak levels and a smaller area under the curve. This was further exacerbated in the MRKO ELS group. This reduced corticosterone release was associated with reduced pituitary POMC mRNA content and increased adrenal weight. These data suggests that ELS deregulates HPA axis (re)activity specifically in females which is further exacerbated by low function of the MR. Presently, stress indices in limbic brain regions are studied in more detail by Western Blotting of MR, GR, and their target genes.
Altogether, our findings support a sex-specific dissociation between early life stress effects on behavior and the stress system and that MR may be an important moderator in shaping stress resilience.

**Disclosures: R.A. Sarabdjitsingh:** None. **V. Bonapersona:** None. **H. Meeusen:** None. **R. Damsteegt:** None. **K. Sparnaaij:** None. **R. de Kloet:** None. **M. Joëls:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.21/LL16

**Topic:** F.04. Stress and the Brain

**Support:** NIMH Grant 1R01MH107556-01

**Title:** Early life adversity and precocial maturation: Sex-specific changes in basolateral amygdala-derived innervation of the prefrontal cortex

**Authors: *J. A. HONEYCUTT**, *J. A. HONEYCUTT, C. DEMAESTRI, S. PETERZELL, H. C. BRENHOUSE
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**Abstract:** Early life experiences significantly shape the behavioral and neural trajectory of an organism across development. Therefore, disruptions during early developmental periods likely set the course for aberrant brain maturation. Indeed, children who have experienced early adversity often exhibit deleterious effects that manifest as maladaptive behaviors, cognitive impairment, and/or increased susceptibility to mental illness. Increasing evidence in humans with a history of adversity points to a role of atypical corticolimbic circuit development, leading to

changes in functional connectivity between the basolateral amygdala (BLA) and prefrontal cortex (PFC). In rodent models of early adversity via maternal separation (MS) during the postnatal period, comparable neural and behavioral phenotypes are observed, including loss of PFC inhibitory tone and increased anxiety-like behaviors. The neural mechanisms underlying these findings following MS remain unknown, though it is likely that dysfunction is in part driven by precocial BLA innervation of the PFC. To determine the impact of sex and MS on this circuitry, targeted anterograde tracer microinjections into the BLA were performed at key developmental milestones spanning juvenility and adulthood. Labeled axonal fibers from BLA-PFC projecting neurons were quantified within the PFC. We present novel data indicating that MS drives increased BLA innervation of the PFC in a sex- and age-dependent manner, such that juvenile MS female innervation patterns resemble that of their adult control counterparts. This suggests a critical role for early experiences on corticolimbic development and provides putative mechanistic insight into the underlying etiology of adversity-induced vulnerability and resilience.

**Disclosures: J.A. Honeycutt:** None. **C. Demaestri:** None. **S. Peterzell:** None. **H.C. Brenhouse:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.22/LL17

**Topic:** F.04. Stress and the Brain

**Support:** Grant AA021262

**Title:** Early Life Stress induces changes in neurometabolic profile in the Hippocampus, mPFC, and Amygdala

**Authors: *T. O. OBISESAN, JR**[1,2], M. C. GONDRE-LEWIS[2,3], P. WANG[4], S. LIN[4]
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**Abstract:** Research has shown that early-life stress at key neurodevelopmental time points has many long-term behavioral implications facilitated by neurochemical and neurostructural alterations. Previous studies from our laboratory implicate maternal separation stress (MS) as an underlying risk factor for anxiogenic, depressive, impulsive, and alcohol-drinking behaviors in rats. However, the conditions, mechanisms, and metabolic activity underlying such changes have yet to be elucidated. Alterations to endogenous oxidant protection system, and unbalancing of excitatory tone in mesocorticolimbic regions have been observed in rat models subjected to early life stress. As such, using this MS rat model we investigated changes of neurometabolite

concentrations in the medial prefrontal cortex (mPFC), amygdala, and hippocampus, which are regions that have been implicated in behavioral deficits observed in MD animals. We assessed micromolar concentrations of 21 metabolites using NMR spectroscopy and a secondary quantitation program called Tarquin. This method allowed us to non-invasively take a wholistic snapshot of the neurometabolic profile of our subjects. Using the raw data and ratios of TNAA(N-acetylaspartate), total choline (TCho), and total creatine (TCr) as internal standards, the concentrations of individual metabolites across animals and treatment groups were compared. In the hippocampus, alanine was found to be increased with exposure to MS, whereas glutathione, aspartate, and total glutamate/glutamine were found to be down regulated in MD animals in a sex specific manner. In the mPFC TCr was upregulated in MS animals when compared to controls. Furthermore, in the mPFC GABA and phosphocholine (PCh) were only upregulated in MD females as compared to Cntl females. The amygdala was the most susceptible to the effects of early life stress, with 12 metabolites being altered by MS stress: creatine, GABA, glutamine, glutamate, NAA, phosphocholine, TNAA, phosphocreatine, total glutamate, and glutamine, total creatine, total choline, and taurine. Changes in the amygdala may be the key metabolic driver for previously observed behavioral deficits associated with defective learning and memory, as well as aberrant affect following MS. Furthermore, alterations in GABA, glutamate/glutamine, glutathione, taurine, and alanine support the assertion that excitatory tone as well as the endogenous oxidant protection systems are targets of MS-induced abnormal metabolism in the hippocampus, mPFC, and amygdala.

**Disclosures: T.O. Obisesan:** None. **M.C. Gondre-Lewis:** None. **P. Wang:** None. **S. Lin:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.23/LL18

**Topic:** F.04. Stress and the Brain

**Support:** RFBR Grant 16-34-00253

**Title:** The effects of early-life stress and histone deacetylase inhibition on maternal behavior in mice

**Authors: *O. V. BURENKOVA**, E. A. ALEKSANDROVA, I. Y. ZARAYSKAYA
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**Abstract:** It is difficult to overestimate the importance of maternal care in the development of the altricial mammalian offspring. For this reason, disturbances in the mother-infant relationship lead to profound short- and long-term negative neurobehavioral effects in both humans and

rodents. Maternal separation (MS) model is one of the most commonly used rodent models of early-life adverse experiences.
To date surprisingly little is known about the effects of MS early in life on maternal behavior in adulthood. Furthermore, the studies with MS shorter than 3 hours are rather scarce, despite the fact that carrying out manipulations with pups during the investigation of the developmental processes (various tests, pharmacological injections, surgical procedures, etc.) always requires MS for the period starting from 30-60 minutes.
The aim of our work was to study the effects of early-life stress, particularly brief repeated MS procedure (MS-only group, 45 min daily on postnatal days (PND) 3-6) and early pain exposure (MS-saline group, saline injections in combination with MS on PND 3-6) on the subsequent maternal behavior of adult females of 129Sv mice. As potential factors involved in effects of MS, we investigated the changes in the behavior of their mothers on the last day of MS and histone acetylation level in the pups' brain after MS. For the prevention of possible occurrence of the negative influences of MS we proposed the use of pharmacological agent, modulating epigenetic mechanisms underlie the long-term effects of early-life experience, i.e. histone deacetylase inhibitor sodium valproate (50 mg/kg s.c. on PND 3-6).
We revealed that even brief periods of MS during the first postnatal week are sufficient to produce alterations in the behavior of adult females. These changes were manifested in a reduction of exploratory behavior (both pup-directed and non-pup-directed) in comparison with intact dams. Analysis of the behavior of their mothers demonstrated the same reduction of exploratory behavior. We also showed that females from the MS-saline group displayed decreased level of maternal grooming and nursing behavior in comparison with intact dams, an effect which was not revealed in the MS-only females. Administration of sodium valproate prevented the occurrence of these negative effects in the MS-saline group.
Considering human data on the impact of child maltreatment on the development of maternal behavior, our models of brief maternal separation and early pain exposure seem to be novel and promising tools for investigation of the mechanisms underlying the effects of early-life adverse experiences. Sodium valproate could be a candidate agent for their prevention.

**Disclosures:** **O.V. Burenkova:** None. **E.A. Aleksandrova:** None. **I.Y. Zarayskaya:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

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**Program#/Poster#:** 504.24/LL19

**Topic:** F.04. Stress and the Brain

**Support:** NIMH Grant T32 MH103213

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**Title:** Early life stress in rats alters cerebellar endocannabinoid dynamics and recognition memory

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**Abstract:** Schizophrenia is a psychotic disorder shown to be more prevalent in low socioeconomic groups with research in human populations implicating stress response dysregulation and, separately, endocannabinoid dysregulation (via cannabis use) in disease onset and exacerbation. Using an animal model, this study explored interactions between the stress response and endocannabinoid systems within the cerebellum, a region dense with the $CB_1$ endocannabinoid receptor and shown to be impaired in schizophrenia.
This study explored behavioral and neural impacts of early life stress in Long-Evans rats reared with or without limited access to bedding during postnatal day (PND) 2-9. Corticosterone (CORT) levels were measured at PND 8 and 70. Rats were assessed on Novel Object Recognition to test memory and Rotarod to evaluate cerebellar integrity at PND 40 and 50, respectively. Lipid analysis was performed on tissue samples of cerebellar interpositus (IP) nucleus via high-performance liquid chromatography and tandem mass spectrometry.
Male rats experiencing early life stress exhibited significantly impaired recognition memory. There were no group differences in Rotarod task performance or CORT levels at PND 8 or 70 across rearing groups, though rats generally exhibited higher CORT levels at PND 70 and females had higher levels overall. At PND 70, male rats experiencing early life stress exhibited a significant decrease in 2-arachidonoyl glycerol (2-AG) and arachidonic acid levels in the IP nucleus compared to normally reared males. Compared to normally reared females, those experiencing early life stress exhibited a significant increase in prostaglandin E2 levels. 2-AG levels were positively correlated with object recognition in males (collapsed across rearing group) and also positively correlated with CORT levels in normal rearing females.
Early life stress, induced by limited bedding, differentially impacted memory in male versus female rats, with males being more impaired. Results suggest that although stress does not alter gross cerebellar function (i.e. motor function via Rotarod task), it appears to alter endocannabinoid dynamics in males in the cerebellar IP nucleus. Further analysis will quantify mRNA for cannabinoid receptors to better characterize aberrations to this system. This work provides a basis for understanding stress impacts on the development of cognitive deficits observed in disorders such as schizophrenia. In the future, we plan to relate these deficits to

impairments in cerebellar-dependent delayed eye-blink conditioning, a robust endophenotype of schizophrenia.

**Disclosures: A.B. Moussa-Tooks:** None. **K. Mackie:** None. **L.A. Bartolomeo:** None. **H. Bradshaw:** None. **E. Leishman:** None. **B.F. O'Donnell:** None. **W.P. Hetrick:** None.

**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.25/LL20

**Topic:** F.04. Stress and the Brain

**Support:** NSERC(Canada) Grant #138199

**Title:** Resting-state functional connectivity of the basolateral amygdala is altered in preweaning rats subjected to chronic early life stress

**Authors: *A. GUADAGNO**[1,3], M. S. KANG[4,1,3], A. P. MATHIEU[2,3], E. GUMA[2,3], G. A. DEVENYI[2,3], P. ROSA-NETO[4,1,3], M. CHAKRAVARTY[2,3], C.-D. WALKER[1,3]
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**Abstract:** Early-life stress (ELS) exposure has life-long consequences for both brain structure and function, and can ultimately impact cognitive and emotional behavior, increasing vulnerability to mental disorders. The basolateral amygdala (BLA) plays an important role in anxiety and fear conditioning and through its wide connections to the prefrontal cortex (PFC) and hippocampus (HIP) in particular, can affect stress reactivity and emotional behavior. However, how ELS affects amygdala function and connectivity in developing rats is unknown. We used the naturalistic limited bedding/nesting (LBN) paradigm to induce chronic stress in the pups between postnatal day (PND) 1-9. Normal bedding (NB) conditions were used as control. Sprague Dawley male NB or LBN rats received structural (FLASH, Resolution 0.1x0.1x0.1mm, TA 23 min) and resting-state functional MRI (rs-fMRI, RAREst, Resolution 0.25x0.25x0.8mm, TR/TE 3000/28 ms, TA 5 min) under <2% isoflurane anesthesia on PND18. All scans were obtained on a Bruker 7T MRI (650 mT/m in 150μs) 24 hrs after treatment with Manganese Chloride ($MnCl_2$, 32 mg/kg, sc), an MRI contrast agent. Three rs-fMRI acquisitions for each animal were preprocessed and registered to a group average anatomical image (FLASH). Each run then generated connectivity maps based on four BLA seeds (left, right, anterior and posterior) using FMRISTATS. The individual connectivity maps were transformed into the template space. All three runs were combined to build a subject level connectivity map. The final results were corrected for multiple comparison using Random Field Theory, $p = 0.05$.

Significantly enhanced contralateral PFC connectivity was found in LBN compared to NB pups from both Left BLA seeds, but only from the Right Posterior BLA. Animals subjected to LBN rearing also exhibited increased connectivity from both Posterior BLA seeds to the contralateral HIP. The ipsilateral connectivity to the HIP was only increased in the Right Posterior BLA, while the Anterior BLA networks tended to show reduced connectivity to the HIP. LBN pups showed greater Left BLA connectivity to the paraventricular nucleus and to the insular cortex. In summary, ELS enhanced BLA-PFC/Hip and insula connectivity in immature preweaning pups with a strong contralateral component. Increased connectivity in these critical nodes of the emotion processing network in developing rats might underlie enhanced fear conditioning and anxiety observed in ELS-exposed adults. Furthermore, most structures displaying enhanced connectivity after ELS are also part of the extended stress circuitry that is recruited under chronic stress in adult animals.

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**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.26/LL21

**Topic:** F.04. Stress and the Brain

**Title:** Sex differences in early postnatal ultrasonic vocalizations and adult hippocampal microglial morphology in California mice (Peromyscus californicus) exposed to paternal deprivation

**Authors: *F. N. MADISON**, A. R. WHITAKER, S. KHANTSIS, E. R. GLASPER
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**Abstract:** Early life stressors, such as childhood neglect and abuse, can increase vulnerability to affective disorders in adult life. It has been well established that variations in rodent maternal care mediates development of affective disorders, therefore early maternal separation has been used as a model to examine the enduring consequences of early adverse life events. Maternal separation has also been shown to induce hippocampal neuroinflammation and long-lasting emotional alterations in rodents. Moreover, auditory communication, such as ultrasonic vocalizations (USVs) emitted by pups over the postnatal period, has been shown to direct maternal responsiveness and increase pup survivability. In biparental species, such as the California mouse (*Peromyscus californicus*), where maternal *and* paternal care is necessary for offspring survival, little is known about the effects of paternal deprivation on pup USVs and adult offspring hippocampal structure. The purpose of this study was to determine to what extent sex differences in USV-directed maternal care across the postpartum period exist in the

biparental California mouse. Additionally, we investigated the relationship among sex, paternal deprivation, and activation of microglia in the adult hippocampus. Offspring were either reared by both parents (controls) or the father was removed on postnatal day (PND) 1 and offspring were reared by the mother alone (paternally-deprived) until weaning. USVs were recorded on PND2, 6, 8, 14, 24, and 30. On PND35, male and female offspring from both groups were weaned and paired housed with same sex conspecifics. On PND60, brains were perfused with 4% paraformaldehyde, sectioned, and immunohistochemically processed for the microglial maker Iba1. A sex difference in USVs during the mid-postpartum period (i.e., PND14) may be present, as paternally-deprived females, on average, emit more vocalizations than control and paternally-deprived males. To what extent sex-dependent differences in USVs, as a result of early life experience, underlies microglial activation remains to be determined. However, irrespective of sex, control mice exhibit more ramified than unramified microglia in the subgranular zone of the dentate gyrus – an effect not observed in PD mice. Taken together, these data suggest that USVs may function to elicit parental care in paternally-deprived females. More so, PD may influence stress-related microglial activation.

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**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 504.27/LL22

**Topic:** F.04. Stress and the Brain

**Support:** NIH grant MD007592

NIH grant DA029989

**Title:** Modification of the ghrelin system by early life stress and environmental enrichment

**Authors: *A. S. PILLAI**[1], G. A. LODOZA[2], J. A. SIERRA FONSECA[3], A. M. RASTEGARI[2], J. N. HAMDAN[4], S. SAUCEDO[1], K. L. GOSSELINK[5]
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**Abstract:** Obesity is a national problem, with nearly 40% of American adults and 17% of children and adolescents characterized as obese. Sex differences also exist, with women having higher rates of obesity than men, but the reasons for this are not fully understood. One factor may be stress, as higher stress levels have been reported in women. The subsequent release of cortisol could affect energy balance and play a role in the development of obesity. Alternatively,

the ghrelin hormone stimulates hunger and increased ghrelin levels have been reported during stress. The ghrelin receptor (GhrR) is expressed in regions of the brain that mediate reward and food intake, but few studies have examined the effects of stress on GhrR expression. The purpose of our study, therefore, was to evaluate the effects of early life stress on hypothalamic GhrR expression in males and females. We also employed environmental enrichment as a countermeasure to protect against the effects of stress. We hypothesized that stress in the neonatal period would persistently increase hypothalamic GhrR expression and that environmental enrichment would prevent this increase. Wistar rat pups were exposed to early life stress in the form of maternal separation (MatSep) for 3h/d on postnatal days (PND) 2-14. Control rats were reared normally. All pups were weaned at PND 21, and allowed to grow to adolescence (PND ~49) or adulthood (PND ~70) before testing. Some groups were weaned into standard living conditions, while others were housed with enrichment bedding, plastic tunnels, and 24h access to a running wheel. The hypothalamic region was dissected from fresh-frozen brain tissue and analyzed for GhrR expression by Western blot, quantified by densitometry normalized to actin. Contrary to our hypothesis, our results indicate a trend toward decreased GhrR expression in the hypothalamus of MatSep rats, but that enriched environmental conditions may in fact be able to reverse this effect. The ability of early life stress to cause long-term modifications to ghrelin action in the brain may be an important factor in stress-induced obesity. On the other hand, our findings confirm and extend our understanding of the role of stress reduction in obesity prevention.

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**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

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**Topic:** F.04. Stress and the Brain

**Support:** NIH grant MD007592

NIH grant DA029989

**Title:** Vulnerability to addiction is increased by early life stress: Dopaminergic effects and synaptic plasticity

**Authors: *J. N. HAMDAN**[1], S. SAUCEDO, Jr.[3], G. A. LODOZA[4], J. A. SIERRA FONSECA[2], L. E. O'DELL[4], K. L. GOSSELINK[4]
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**Abstract:** Stress has been shown to play a role in increasing the incidence and progression of addictive behaviors, making it a concern for the roughly 1.2 million people nationwide who suffer from methamphetamine (Meth) addiction. When stress is experienced during early life, it can persistently alter brain function and increase drug-taking behaviors and risk for addiction in adults. It is not fully understood how stress can mediate changes in drug taking behavior, or how early life stress impacts drug taking behavior in adulthood. The goal of this project, therefore, was to examine molecular changes in the brain that are induced by early life stress and may enhance vulnerability to Meth addiction. Our hypothesis was that stress in the postnatal period would increase the expression of proteins involved in dopaminergic signaling in the reward circuitry. We further hypothesized that stress would decrease the expression of proteins associated with synaptic function and plasticity in brain regions involved in memory and executive function. Male Wistar rats were maternally separated (MS) from their dams for 3h/d on postnatal days 2-14 and assessed as adults. Brain tissues were harvested and the prefrontal cortex (PFC), hippocampus, caudate-putamen (CPu), and nucleus accumbens (NAcc) dissected and evaluated for protein expression by Western blot. The markers examined were: dopamine transporter (DAT), dopamine receptor-1 ($D_1$), dopamine receptor-2 ($D_2$), tyrosine hydroxylase (TH), post-synaptic density 95 (PSD95), NMDA receptor-1 (NMDAR1), and α-synuclein. A significant increase was seen in the expression of $D_2$ in the NAcc of MS rats, while there was a trend toward increased expression of TH and $D_2$ in CPu ($p=0.10$ and $p=0.13$ respectively) and decreased expression of NMDAR1 in PFC ($p=0.07$) and α-synuclein in hippocampus ($p=0.08$). Separate groups of MS animals were behaviorally tested for conditioned place preference (CPP) with 1 mg/kg Meth to identify changes in drug sensitivity caused by MS. Stressed animals did show CPP, but did not demonstrate a difference in preference for Meth compared to controls. Future studies will test responses to different doses of Meth in the CPP paradigm, but our current findings partially support our hypothesis in that long-term changes in dopaminergic and synaptic function were seen or suggested following early life stress.

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**Poster**

**504. Early-Life Stress: Neurophysiological and Neurochemical Consequences**

**Location:** Halls A-C

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**Topic:** F.04. Stress and the Brain

**Support:** NIH Grant NS064571

NIH Grant UL1TR000135

**Title:** The proinflammatory cytokine TNFa alters neural network activity by injuring GABAergic interneurons

**Authors: *E. TRIPLET**, R. LAFRANCE-COREY, K. MIRCHIA, H.-L. WANG, G. WORRELL, C. HOWE
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**Abstract:** Neuroinflammation plays a critical pathogenic role in numerous diseases of the CNS, ranging from traumatic brain injury and multiple sclerosis to epilepsy and Alzheimer disease. Neuroinflammation is associated with local activation of microglia and astrocytes and with infiltration of immune effectors such as monocytes and neutrophils. A common mechanism-of-action shared by these effectors is release of proinflammatory cytokines such as TNFα, IL6, IL1β. Using a murine model of acute CNS viral infection, we have shown that the infiltration of inflammatory monocytes triggers severe injury to CA1 pyramidal neurons in the hippocampus. This injury is associated with seizures and with permanent cognitive impairment. However, despite our understanding of the kinetics of inflammatory monocyte infiltration, CA1 pyramidal neuron injury, seizure evolution, and behavioral sequelae, and despite reports from others showing that IL6 and other cytokines are involved in hippocampal injury in this model system, we do not know the underlying pathogenic mechanisms responsible for disruption of the hippocampal neural circuit.
Preliminary experiments in mice infected with the Daniel's strain of Theiler's murine encephalomyelitis virus indicate that hippocampal parvalbumin-positive GABAergic interneurons are preferentially lost during acute infection. Electrophysiological analysis of long term potentiation in hippocampal slices from infected mice reveals a reduction in GABAergic tone at the Schaffer collateral inputs into CA1. These outcomes are associated with the production of TNFα by inflammatory monocytes, as assessed by flow cytometry, multiplexed cytokine analysis, ELISA, and analysis of hippocampal interstitial fluid sampled by microdialysis. In vitro stimulation of murine hippocampal neural networks with TNFα induces profound changes in spontaneous and evoked calcium transients, as assessed by imaging of neurons transduced with an AAV9 vector driving synapsin promoter-dependent expression of the GCaMP6f calcium reporter. Finally, high-density, high-frequency measurement of field potentials in hippocampal neural networks via multielectrode array analysis indicates that GABAergic tone is rapidly modulated by TNFα and other inflammatory cytokines, suggesting that such factors play a fundamental role in the induction of seizures and disruption of cognition in CNS diseases associated with neuroinflammation.

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**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

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**Topic:** F.04. Stress and the Brain

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**Title:** Pubertal stress programs a long-term, sex-specific disruption of the HPA axis

**Authors: *K. E. MORRISON**, T. L. BALE
Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Adverse childhood experiences are one of the greatest predictors for affective disorder presentation for women. As the puberty transition is marked by hormonal changes and ensuing reorganization of the brain and periphery, it may represent a window of vulnerability for adversity to result in long-term programming. Periods of hormonal flux in the female lifespan, including pregnancy, exacerbate the risk for affective disturbances and promote hypothalamic-pituitary-adrenal (HPA) axis dysregulation, a key feature of affective disorders. However, little is understood as to how stress experienced during the pubertal transition alters ongoing brain maturation and its interaction with later-life events, such as pregnancy. We have established a translationally relevant mouse model in which peripubertal stress results in a blunted corticosterone response to acute restraint stress only during pregnancy in females, but produces no effect in males. This suggests that HPA programming by peripubertal stress in females intersects with the state of pregnancy to expose dysregulation. RNA-Seq analysis of the paraventricular nucleus of the hypothalamus (PVN) during pregnancy revealed a reprogramming of gene expression by peripubertal stress, including changes in the GABA system. As the GABA system is critical in regulating PVN responsiveness and is modulated by allopregnanolone, we hypothesized that the rise in allopregnanolone during pregnancy is responsible for eliciting the HPA axis dysregulation. Female mice were exposed to chronic variable stress (CVS) from postnatal days 21-34, and we examined the corticosterone response to acute restraint stress during late pregnancy. Pharmacological reduction of allopregnanolone by systemic injection of indomethacin resulted in the recovery of a normal corticosterone response in CVS females. Importantly, the blunted corticosterone response was recapitulated in CVS adult males treated with allopregnanolone, further supporting a role for this neurosteroid. Preliminary data suggests that disrupting allopregnanolone binding at the GABA-A receptor in the PVN leads to similar recovery of a normal HPA axis response in CVS females. Previous RNA-Seq findings suggest

that the changes in the GABA system are maintained by epigenetic modifications induced by CVS. To address this possibility more directly, effects of peripubertal stress on histone marks in the PVN in both virgin and pregnant adults were examined. Together, these studies provide novel insight into the mechanisms underlying female-relevant risk factors for stress dysregulation, a central endophenotype of affective disorders.

**Disclosures: K.E. Morrison:** None. **T.L. Bale:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.02/LL26

**Topic:** F.04. Stress and the Brain

**Support:** MH099910

MH104184

MH108286

**Title:** Mechanisms of paternal stress programming of neurodevelopment via dad's epididymis

**Authors: *J. CHAN**, N. V. BHANU, B. A. GARCIA, T. L. BALE
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**Abstract:** Paternal exposures to environmental insults such as stress, diet, drugs or toxins have been linked with increased risk of neuropsychiatric disease in subsequent generations. Recent studies using rodent models have shown that paternal exposure to a variety of perturbations can impact offspring behavior and physiology, and have identified changes in histone modifications, DNA methylation, and/or small non-coding RNAs in sperm as potential mechanisms of transmission. However, the mechanism by which paternal environmental exposures reprogram sperm epigenetic marks to subsequently influence offspring development is not known. We have developed a paternal stress model in which chronically stressed males sire offspring with a significantly blunted stress response as adults. Sperm analyses identified a significant increase in 9 microRNA (miRs) following paternal stress exposure. Zygote microinjection of these miRs recapitulated the offspring stress phenotype, providing a functional role for sperm miRs. Our current studies examine the mechanism and timing by which chronic stress alters sperm miRs. Remarkably, studies in our mouse model reveal that males bred 3 months following stress exposure continue to produce offspring with altered stress reactivity, suggesting lasting effects of experience on intergenerational transmission. To determine where in the sperm development or maturation process stress-mediated changes occur, we compared reproductive tissue miR expression where transcriptional assessment revealed upregulation of the same stress-sensitive

miRs found in sperm in the caput epididymis, suggesting that the caput is involved in programming of sperm miRs. Moreover, levels of glucocorticoid receptor (GR) were specifically increased in the caput months after stress end, suggesting GR may play a role in long-term programming. Interestingly, extracellular vesicles (EV) from the caput have been suggested to fuse and alter RNA expression in maturing sperm. To determine if stress alters caput EV miR expression, we developed an *in vitro* model of chronic corticosterone treatment using caput epithelial cells. We show that our model mimics aspects of chronic stress programming *in vivo*, including increases in GR levels long-term. Remarkably, we show that chronic corticosterone treatment alters caput EV miR expression, suggesting a mechanism by which the caput may communicate stress programming to sperm. These studies suggest that paternal experiences can have lasting changes on the germline and future offspring brain development, and offer an exciting novel mechanism by which the environment can dynamically regulate sperm epigenetic marks.

**Disclosures:** **J. Chan:** None. **N.V. Bhanu:** None. **B.A. Garcia:** None. **T.L. Bale:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.03/LL27

**Topic:** F.04. Stress and the Brain

**Support:** MH099910

MH108286

MH104184

MH087597

MH091258

**Title:** Placental H3K27me3 promotes female resilience to prenatal insults

**Authors: *C. M. O'DONNELL**[1], B. M. NUGENT[2], T. L. BALE[2]
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**Abstract:** Prenatal stress is a risk factor for male-biased neurodevelopmental disorders, including early onset schizophrenia and autism. In our mouse model of early prenatal stress (EPS), stress exposure during the first week of gestation imparts long-term HPA stress axis, metabolic and cognitive deficits to male offspring. The placenta, a fetally-derived tissue reflecting fetal sex chromosome complement, provides necessary factors for early brain

development. Thus, sex differences in placental function might radically influence sex biases in neurodevelopmental vulnerability to prenatal insults. We previously identified the X-linked, stress sensitive, nutrient sensor O-linked-N-acetylglucosamine (OGT) as a critical mediator of the sex-specific effects of prenatal stress on offspring brain development. OGT modifies several epigenetic regulators including the H3K27me2/3 methyltransferase, EZH2. In mouse placentas with trophoblast-specific OGT reduction, we found that OGT determines higher protein levels of H3K27me3 in females and genome-wide sex differences in H3K27me3 patterns. We hypothesized that female-biased epigenetic repression (i.e. H3K27me3) protects females from prenatal insults such as EPS. To test this hypothesis, we reduced H3K27me3 in female placentas using trophoblast-specific manipulations of EZH2 and exposed these females to EPS. Decreasing placental EZH2, and H3K27me3, created female vulnerability to the effects of EPS, sensitizing their HPA axis reactivity and causing long-term changes in body weight. To evaluate the role of the X and Y -linked H3K27 demethylases in establishing sex differences in H3K27me3 and confirm the role of H3K27me3 in male risk and female resilience to the neurodevelopmental deficits associated with EPS exposure, we generated trophoblast-specific mouse lines with reducible UTX and inducible UTY. We predict that reducing UTX in male trophoblasts will augment placental H3K27me3 and protect males from sensitivity to prenatal insults. In addition, we predict that reducing UTX while inducing UTY expression in female trophoblasts will masculinize genome-wide H3K27me3 patterns and masculinize placental responses to environmental perturbations. These studies, aimed at elucidating the basic biological differences between male and female developmental programs, bring us closer to fully understanding the etiology of sex-biased neurodevelopmental disorders.

**Disclosures:** **C.M. O'Donnell:** None. **B.M. Nugent:** None. **T.L. Bale:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.04/LL28

**Topic:** F.04. Stress and the Brain

**Support:** MH091258

MH087597

MH104184

MH108286

MH099910

**Title:** Circulating extracellular vesicles are novel mediators of sex differences in neurodevelopment

**Authors: *B. M. NUGENT**[1], J. M. FLUHARTY[1], T. L. BALE[2]
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**Abstract:** Understanding how prenatal stress alters the fetal milieu in a sex-specific manner is important for identifying mechanisms involved in perturbations of brain programming, which are often associated with sex-biased neurodevelopmental disorders. In our well-established mouse model, male offspring exposed to early prenatal stress (EPS) have altered hypothalamic pituitary axis (HPA) programming, resulting in increased stress sensitivity and dysregulation in hypothalamic metabolism, endophenotypes identified in boys with autism and men with early-onset schizophrenia. Importantly, our EPS protocol occurs during the first week of gestation, prior to brain development and thus likely alters programming of peripheral tissues in addition to altering neurodevelopmental processes. Previously, our lab found that gene sets important for endo- and exosomal cellular processes were down regulated in the male placenta in response to EPS, suggesting that EPS alters fetal extracellular vesicle (EV) signaling. EVs are small vesicles secreted locally and into the bloodstream by most tissues. EVs transfer proteins, microRNAs, and other signaling factors between cells and tissues as a means of short- and long-distance communication. Using proteomics and small RNA-Seq, we found that EPS exposure altered the miRNA and protein content of EVs in fetal and neonatal circulation. We predict that these alterations in EV cargo contribute to sex differences in programmatic events in the developing brain. Using near infrared *in vivo* and confocal imaging of labeled EVs, we identified sex differences in the accumulation and cellular localization of peripheral exosomes in the developing brain, which are altered by EPS exposure. To assess the direct mechanistic effects of EPS-altered peripheral EVs on brain development, we isolated EVs from control and EPS-exposed neonates and injected these vesicles into age and sex-matched naïve neonates. We found that EVs derived from EPS-exposed males promoted long-term changes in male body weight, HPA stress axis sensitivity and behavior, although female EPS EVs had no long-term programmatic effects. Further, we analyzed RNA-Seq from hypothalamic punches from naïve neonates injected with EVs derived from control and EPS-exposed neonates. This allowed us to link individual EV miRNAs with changes in mRNA expression in the developing brain, and to identify specific vesicular miRNAs important for brain development. Overall, our findings demonstrate that circulating extracellular vesicles contribute to sex-specific neurodevelopmental programming. *Supported by MH091258, MH087597, MH099910, MH104184 and MH108286.*

**Disclosures:** **B.M. Nugent:** None. **J.M. Fluharty:** None. **T.L. Bale:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.05/LL29

**Topic:** F.04. Stress and the Brain

**Support:** NIH MH109298

NIH P50-MH099910

NIH MH104184

NIH MH091258

NIH MH087597

NIH MH073030

NIH MH108286

**Title:** The maternal microbiome plays a causal role in programming offspring gut-brain development

**Authors: *E. JAŠAREVIC**[1], C. HOWARD[1], K. E. MORRISON[1], A. MISIC[1], T. WEINKOPFF[1], P. SCOTT[1], C. HUNTER[1], D. BEITING[1], T. L. BALE[2]
[2]Dept of Biomed. Sci., [1]Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Prenatal stress is associated with an increased risk for neurodevelopmental disorders. In our established mouse model of early prenatal stress (EPS), lasting reprogramming on offspring development have been demonstrated, including reprogramming of the hypothalamic-pituitary-adrenal (HPA) axis, dysregulation of HPA stress axis responsivity, and post-pubertal growth. Mounting evidence points to an influence of maternal stress experience on reprogramming of the gut-brain axis via the maternal vaginal microbiome. To provide a causal link of the stress-altered vaginal microbiota with reprogramming of the developing gut-brain axis, we used cesarean delivery and oral gavage of neonate mice colonized with vaginal microbiota from either control or EPS dams, and assessed for recapitulation of the EPS phenotype. By manipulating microbial colonization of the neonate gut, we reveal an exciting causal role of the maternal vaginal microbiome in promoting sex-specific recapitulation of neuroendocrine dysfunction observed in our EPS model, including HPA stress axis dysregulation and metabolic alterations. Surprisingly, colonization with a normal microbiome at birth failed to rescue EPS phenotypes, suggesting critical reprogramming of the fetal intestinal niche preceding colonization. Gene set enrichment analysis revealed robust sex-specific differences in gene sets

involved in normal immune function, whereby the expression of genes within these gene sets were disrupted in EPS males, but not females. As sex-specific enrichment of genes involved in innate immunity may reflect functional differences in immune cell populations present in the EPS fetal intestine, we used multicolor flow cytometry to demonstrate sex-specific disruption of EPS on the frequency of immune cell populations in the fetal intestine. To examine the hypothesis that maternal stress reprogramming may render male offspring more vulnerable to additional stressors throughout the lifespan, we used a second hit protocol in which offspring were exposed to chronic stress and programmatic effects on the gut-brain axis were assessed. Analysis revealed a robust disruption of the intestinal barrier. In addition, dysregulation of energy metabolism and neurotrophin signaling pathways was detected in the PVN of stress-exposed EPS males, reflecting potential deficits in neuroplasticity that impacts neuroendocrine function and ability to respond and adapt to external stimuli in these males. Taken together, these studies provide a novel mechanism by which maternal stress experience during pregnancy reprograms the gut-brain axis and confers sex-specific disease risk throughout life.

**Disclosures:** **E. Jašarevic:** None. **C. Howard:** None. **K.E. Morrison:** None. **A. Misic:** None. **T. Weinkopff:** None. **P. Scott:** None. **C. Hunter:** None. **D. Beiting:** None. **T.L. Bale:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.06/LL30

**Topic:** F.04. Stress and the Brain

**Support:** United States-Israel Binational Science Foundation

**Title:** Adolescent stress alters fear conditioning and glucocorticoid receptor expression in basolateral amygdala

**Authors: *R. A. SKIPPER**, C. L. WELLMAN
Dept. of Psychological and Brain Sci., Indiana Univ. Bloomington Dept. of Psychological and Brain Sci., Bloomington, IN

**Abstract:** In humans, early life adversity can lead to a host of debilitating outcomes, including anxiety and depression. This has been modeled in rodents: we have previously shown that a single early life stressor permanently alters emotional learning, fear extinction, and dendritic plasticity in the basolateral amygdala (BLA; Quinn et al., 2015; Skipper et al., in prep). These enduring stress effects are correlated with altered neuroendocrine function. Adolescent stress produces extreme fluctuations in stress hormone levels, which could permanently alter the stress response to produce lasting behavioral changes (Romeo et al., 2016). However, little research

has been done to assess the short-term effects of acute early life stress. Additionally, as many stress-related disorders are more prevalent in women than men, an investigation of sex differences in these effects is warranted. The current experiments assess the short-term effects of acute stress on adolescent fear conditioning and glucocorticoid receptor (GR) expression in the BLA. Male and female rats underwent a 30-minute elevated platform stressor on postnatal day 25 (P25); unstressed controls underwent a similar handling procedure, without stress exposure. On P26, all animals received three tone-shock pairings. Fifty minutes later, brains were collected for immunohistochemistry. Sections were incubated in GR antibody (M-20; Santa Cruz Biotechnology), and immunoreactivity was detected using nickel-enhanced DAB. To quantify GR expression, optical density of each labeled cell within nine 2500 $\mu m^2$ sampling regions evenly spaced through the rostral-caudal extent of BLA was measured and expressed relative to background optical density. Though no behavioral differences were observed during tone presentations, an interesting pattern of results emerged during the 30-second period following each tone. Among unstressed animals, males were significantly more active than females, and this sex difference was abolished by prior stress exposure. This was due to behavioral suppression among males; females showed high levels of freezing and low levels of inter-trial activity that were unaffected by prior stress exposure. Preliminary data suggest that GR levels are higher in the BLA in unstressed males compared to females, and that stress suppresses GR expression selectively in males. Thus, stress may induce different patterns of GR expression in males and females that map onto sexually dimorphic behavioral phenotypes during conditioning. These preliminary findings suggest that sex-dependent stress effects on conditioning in adolescents may be mediated by alterations in expression of GR in the BLA.

**Disclosures: R.A. Skipper:** None. **C.L. Wellman:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.07/LL31

**Topic:** F.04. Stress and the Brain

**Support:** NIH grant MD007592

**Title:** Impaired proteostasis in rat hippocampus and cortex in response to early life stress

**Authors: *J. A. SIERRA FONSECA**[1], J. N. HAMDAN[2], G. A. LODOZA[2], S. SAUCEDO, Jr.[3], K. L. GOSSELINK[2]
[1]Biol. Sci., Univ. of Texas At El Paso, El Paso, TX; [3]Biol. Sci., [2]Univ. of Texas at El Paso, El Paso, TX

**Abstract:** Adverse events that occur early in life have been shown to enhance vulnerability to neurodegeneration in later years. Early life stress (ELS) can induce persistent neurochemical changes that ultimately disrupt neuronal circuits and functions. Among these changes are misfolded and aggregated proteins, hallmarks of several neurodegenerative diseases. In the normal brain, proteolysis is critical to maintain proteostasis, which includes the clearance of abnormal proteins by the ubiquitin-proteasome system (UPS) and the autophagy-lysosomal pathway (ALP). Using ubiquitin as signal, the UPS degrades soluble, short-lived proteins through the proteasome. The ALP is a bulk degradative pathway that involves autophagosome fusion with the lysosome for cellular component destruction and recycling. Accumulating evidence suggests that that these two systems become impaired in neurodegeneration, causing abnormal protein aggregation and leading to irreversible neuronal damage and death. It is known that stress can influence the development and progression of neurodegenerative diseases, yet the underlying mechanisms for this remain poorly understood. We therefore hypothesized that ELS reduces proteolysis in the brain, leading to deficient clearance and subsequent accumulation of abnormal proteins. Wistar rats underwent ELS in the form of maternal separation (MS) for 3h/d on postnatal days 2-14. Brain tissues were then harvested from adults, and hippocampal and cortical regions isolated and evaluated for proteins associated with the UPS and ALP pathways by Western blot. ALP markers (LC3 and p62), UPS markers (20S and 26S proteasome and K48 polyubiquitinated proteins), and disease-associated markers (Tau, phospho-Tau, α-synuclein, and Parkin) were examined. In hippocampus, ALP markers significantly increased following MS. UPS marker expression exhibited sex differences, with increased expression of 20S proteasome and K48 polyubiquitinated proteins in females but decreased expression in males. In hippocampus, phospho-Tau (pSer262 and pThr231) was increased significantly after MS in females, α-synuclein decreased in males and increased in females, and Parkin increased significantly in both sexes. Interestingly, none of the markers showed significant changes in cortical homogenates. Taken together, our results indicate that ELS can selectively modify the protein degradation machinery in different brain regions, which could impact abnormal protein accumulation and the development of neurodegenerative disease.

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**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** F.04. Stress and the Brain

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**Title:** Up-regulation of GLT-1, a glutamate transporter, expressed within glutamatergic axon terminals & on the plasma membrane of astrocytic processes abutting excitatory synapses in the hippocampus contributes to resilience of adolescent female C57BL6/J mice to food restriction-evoked hyperactivity in an animal model of anorexia nervosa relapse

**Authors: *C. J. AOKI**, A. D. SHERPA, O. BILASH, A. A. NAIK
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**Abstract:** Severe voluntary food restriction (FR) is the defining symptom of anorexia nervosa, but anxiety, excessive exercise, and maladaptive decision-making contribute to its severity and relapse vulnerability. We are able to quantify these behavioral hallmarks in a mouse model, called activity-based anorexia (ABA). When wheel-acclimated adolescent mice have their food access restricted, they greatly augment their wheel running, choosing to run even during the hours of food access, hence displaying voluntary FR. The ABA model can be extended to also capture relapse, by following 3 days of restricted food access ($1^{st}$ ABA) with 7 days of recovery, then of 4 more days of restricted food access ($2^{nd}$ ABA). While the great majority of mice exhibit FR-evoked hyperactivity during the $1^{st}$ ABA, some even to the point of lethality, only about half exhibit FR-evoked hyperactivity during the $2^{nd}$ ABA (relapse). What might be the cellular and molecular bases for the resilience that is acquired by some but not others between the $1^{st}$ and $2^{nd}$ ABA? **We hypothesize** that excessive excitability of pyramidal neurons in the hippocampus underlies severity of ABA, while up-regulation of molecules that suppress excitability underlie resilience. In support of this hypothesis, we have observed that excitatory synapses of rodent hippocampal pyramidal neurons exhibit heightened levels of synaptic NR2B-NMDA receptors (NR2B-NMDARs) following one ABA induction (DOI:10.1007/s00429-016-1341-7) and that the increased *levels* correlate with severity of individual animals' weight loss. Here, we used electron microscopy to show that animals resilient to relapse exhibit up-regulation of GLT-1 in the hippocampus. ABA relapse vulnerability was quantified in 7 animals, based on the extent of increase in voluntary wheel running during the $2^{nd}$ ABA. This value ranged from 0 to 18 km/day among the animals during the $2^{nd}$ ABA. Pearson's analyses revealed a strong correlation ($p<0.05$) between this measure of individuals' ABA relapse vulnerability and GLT-1 immunoreactivity in glutamatergic axon terminals and astrocytic plasma membranes immediately adjacent to axo-spinous synapses. This correlation was negative ($r=-0.8$ for astrocytes and axon terminals), indicating that individuals with the least vulnerability were the ones that expressed the highest levels of GLT-1 at excitatory synapses. Augmentation of GLT-1 can dampen hippocampal excitability by removing extracellular glutamate and minimizing

NR2B-NMDAR currents. These findings suggest that antibiotics, which increase GLT-1 expression, may be helpful for putting a break on the maladaptive behavior of anorexia nervosa.

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**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** F.04. Stress and the Brain

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**Title:** Distinct populations of calbindin neurons modulate susceptibility and resilience to the effects of early-life stress

**Authors: *X.-D. WANG**[1], J.-T. LI[2], X.-M. XIE[2], J.-Y. YU[1], T.-M. SI[2]
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**Abstract:** As a $Ca^{2+}$ buffer, sensor and transporter, calbindin critically modulates synaptic plasticity. The reduction of calbindin in hippocampal neurons has been implicated in cognitive disorders, including those induced by early-life stress. However, it is unclear how early-life stress modulates calbindin expression in distinct populations of hippocampal neurons and the contribution of each calbindin-expressing neuronal population to memory. Here, we report that hippocampal excitatory and inhibitory calbindin neurons, respectively, modulate the susceptibility and resilience to early postnatal stress-induced spatial memory deficits. The temporal expression profile of hippocampal calbindin coincided with the critical developmental period of the hippocampus. Stress exposure during this stage lastingly reduced calbindin levels in all CA1 and DG neurons. Reduced calbindin levels in CA1 or DG excitatory neurons, but not CA1 interneurons, strongly correlated with spatial memory impairments. Accordingly, selective knockdown of calbindin in CA1 or DG excitatory neurons mimicked postnatal stress-induced memory deficits in adulthood. By contrast, although calbindin knockdown in CA1 interneurons did not disrupt memory under basal conditions, it preserved memory after an acute stress

challenge. Moreover, calbindin expression levels were suppressed by early-life stress through the cell adhesion molecule nectin3, and in turn reduced IMPase levels. Our findings highlight calbindin as a key molecule for the reprogramming effects of early-life stress on cognition, and exemplify how distinct neuronal populations sharing a same molecule confer the susceptibility or resilience to stress.

**Disclosures:** **X. Wang:** None. **J. Li:** None. **X. Xie:** None. **J. Yu:** None. **T. Si:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.10/MM1

**Topic:** F.04. Stress and the Brain

**Title:** Early-life stress causes a heightened state of trigeminal nociception and gut dysbiosis: Evidence of risk factor for development of chronic orofacial pain conditions

**Authors: *L. CORNELISON**[1], O. PETERSON[1], J. L. HAWKINS[2], P. L. DURHAM[3]
[2]JVIC/CBLS, [3]JVIC-CBLS, [1]Missouri State Univ., Springfield, MO

**Abstract:** Objective: The goal of our study was to examine the effects of secondary traumatic stress on trigeminal nociception and the diversity of the gut microbiota.
Background: Secondary traumatic stress is described as sensitization in a naïve individual elicited through exposure to an individual who directly experienced some trauma. Early-life stress can promote development of a hypervigilant state and increase the risk of developing a chronic orofacial pain such as migraine or temporomandibular disorder (TMD). There is emerging evidence of the importance of the gut-brain axis in health and disease progression. In support of this notion, gut dysbiosis is associated with multiple neurological diseases. Knowledge of the relationship between increased nociceptive signaling in the trigeminal system and the gut microbiota is essential to better understand the gut-brain axis and subsequent negative health outcomes associated with gut dysbiosis.
Methods: Adult Sprague-Dawley male sender rats were subjected to a water immersion apparatus (primary traumatic stress) and returned to their cages, which were placed next to breeding, pregnant, or nursing female rats that served as receiver rats (secondary traumatic stress). Offspring from receiver rats were allowed to develop until young adults at which time the animals were tested for nocifensive response to mechanical stimulation in two facial areas using von Frey filaments and Durham animal holder. In addition, bacterial diversity in fecal and cecal samples collected from naive and stressed F1 generation (>45 days old) animals was determined by next-generation sequencing.
Results: Early-life stress mediated an increase in the average number of nocifensive responses over the eyebrow and masseter muscle when compared to the level of sensitivity in naïve

offspring, and the effect was greater in females. Both male and female offspring of mothers co-housed with stressed males had lower bacterial diversity, as well as reduced percentages of commensal bacteria, in their fecal and cecal samples when compared to offspring of unstressed animals. More specifically, there was a reduction in the amount of Lactobacillus and Bacteroides in the stressed offspring.
Conclusion: Results from our study demonstrate that early-life secondary stress induces an enhanced level of nociception of trigeminal neurons that temporally correlated with pathophysiological changes in the gut microbiota. Furthermore, our findings provide evidence that early-life stress can promote development of a hypervigilant trigeminal system and gut dysbiosis, pathophysiological conditions associated with chronic orofacial pain conditions.

**Disclosures: L. Cornelison:** None. **O. Peterson:** None. **J.L. Hawkins:** None. **P.L. Durham:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.11/MM2

**Topic:** F.04. Stress and the Brain

**Support:** R37 AA08757

**Title:** Binge-like alcohol produces long-lasting epigenetic marks on the proopiomelanocortin gene and the stress axis only during the prenatal to prepubertal period but not after puberty

**Authors: O. GANGISETTY**[1], S. MURUGAN[2], M. CABRERA[2], L. CHASTAIN[2], *D. K. SARKAR[2]
[1]Endocrine Program, Rutgers Univ., New Brunswick, NJ; [2]Rutgers, SUNJ, New Brunswick, NJ

**Abstract:** Alcohol exposure (either prenatally or in the early postnatal period) can impact developmental pathways resulting in lasting structural and regulatory changes that predispose individuals to adulthood diseases including long-term hyper-responsiveness to stress with exaggerated circulating glucocorticoids and enhanced anxiety and depression like behaviors. Recently, it has been shown that alcohol exposures during the adolescent periods similarly predisposes individuals to adulthood stress abnormalities including long-term hyper-responsiveness to stress with exaggerated circulating glucocorticoids and enhanced anxiety. This raises the question of developmental timing: when does alcohol programming of stress axis to hyper-response cease? To address this issue we fed young rats at various stages of reproductive development (postnatal period 2-7 days of age; juvenile periods, 15-20 days of age; prepubertal period 23-28 days of age; or post-pubertal period 50-55 days age) with a liquid diet containing 11.34% alcohol to raise blood alcohol levels to a range of 150-200mg/dl. Control animals were

pair-fed an isocaloric volume of maltose dextrin. These rats were maintained in the animal house and challenged with restraint stress around 70 days of age. The stress challenge was conducted in both sexes. For females, the stress study was conducted on diestrus. Several days after the stress response, animals were sacrificed and the mediobasal hypothalamic tissue samples were obtained and used for measurements of proopiomelanocortin (Pomc) DNA methylation and Pomc gene expression. Determination of plasma glucocorticoid levels after restraint demonstrated an enhanced response to restraint stress in adult male and female rats who were given alcohol either on postnatal, juvenile or prepubertal period but not after pubertal period. Since Pomc is known to be an inhibitory regulator of the stress axis, we measured the expression of Pomc mRNA and DNA methylation levels and found reduced expression of Pomc but increased methylation of Pomc gene in rats treated with alcohol on postnatal, juvenile or prepubertal period but not after pubertal period. These results identify a critical period for alcohol programming of the stress axis via epigenetic mechanism of Pomc promoter hypermethylation during the developmental period.

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**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.12/MM3

**Topic:** F.04. Stress and the Brain

**Support:** Pharmacology Department Hypertension Pilot Grant

K08-MH086812-06

T32-NS007421

**Title:** The impact of a vasopressin model of preeclampsia on neurodevelopment and neuroimmune outcomes in mouse offpsring

**Authors: *S. B. GUMUSOGLU**[1,2], A. CHILUKURI[1], S. HAIDER[1], S. SCROGGINS[1], J. SANDGREN[1], M. SANTILLAN[3], D. SANTILLAN[3], J. GROBE[4], H. E. STEVENS[2]
[2]Psychiatry, [3]Obstetrics & Gynecology, [4]Pharmacol., [1]Univ. of Iowa, Iowa City, IA

**Abstract:** Background:
Preeclampsia is an often severe, gestational hypertensive condition linked to abnormal child neuropsychiatric outcomes (e.g. autism). This connection between preeclampsia and offspring neurodevelopment is poorly understood. One unique animal model of preeclampsia involves continuous maternal administration of arginine vasopressin (AVP) across pregnancy. Here, we examine whether this model results in altered neurodevelopment and neuroinflammation in

prenatally exposed offspring.
Method:
C57Bl/6J mouse dams were implanted with a subcutaneous osmotic minipump, filled with AVP or saline (administration rate: 24 ng/hr), 3 days prior to mating. Offspring brains were collected at embryonic day 14 (E14), E18, day of birth (P0), postnatal day 7 (P7), and in adulthood, sectioned, mounted, stained for microglia (Iba-1, CD68), and counterstained for nuclei (DAPI). Cortical anatomy and neuroimmune changes were examined. Adult offspring were tested for behavioral phenotypes using the Y-Maze, rotarod, social approach, and elevated plus maze assays.
Results:
Preeclampsia exposed adult males exhibited increased anxiety-like behavior and altered social behavior while adult females exhibited impaired procedural learning and working memory. Preeclampsia exposed males exhibited reduced cortical volume, particularly in deep layers, at E18 and P0 despite showing no changes in cortical plate volume at E14. Volume reductions were also seen to persist at P7 and 3 months of age. Lastly, preeclampsia exposed offspring exhibited increased levels of the pro-inflammatory cytokine IL-17 at E18 and altered cortical microglia in pre- and post-natal brain.
Conclusions:
Within an AVP-based model of preeclampsia, we found that exposed offspring exhibited a constellation of sex-specific, aberrant behavior, suggestive of altered corticogenesis. Exposed male offspring demonstrated reduced cerebral cortex volume, beginning in late gestation, which persisted into adulthood. These offspring also exhibited a pro-inflammatory phenotype, indicated by cytokine and microglia changes. We plan to use this preeclampsia model to understand the maternal physiological mechanisms, immune cascades, and sex-differences underlying these altered offspring phenotypes.

**Disclosures: S.B. Gumusoglu:** None. **A. Chilukuri:** None. **S. Haider:** None. **S. Scroggins:** None. **J. Sandgren:** None. **M. Santillan:** None. **D. Santillan:** None. **J. Grobe:** None. **H.E. Stevens:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.13/MM4

**Topic:** F.04. Stress and the Brain

**Title:** Effects of early life stress and chronic fluoxetine administration on the expression of endogenous opioid genes in c57BL/6J mice

**Authors: *B. D. SACHS**[1,2], A. BUNCHER[1], K. DODSON[1]
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**Abstract:** A history of early life stress (ELS) is a significant risk factor for a number of neuropsychiatric disorders, but the mechanisms through which early life stressors contribute to the development of mental illness remain largely unknown. It has been hypothesized that long-lasting changes in gene expression induced by ELS might underlie this increased vulnerability to psychiatric disorders, but the specific transcriptional alterations that underlie the negative consequences of ELS have not been entirely identified. Aberrant endorphin signaling has been implicated in several long-term responses to ELS, and thus identifying ways to reverse the effects of ELS on the endogenous opioid system may have therapeutic potential in the treatment of several psychiatric conditions. In the current study, we used c57/BL6J mice to examine the effects of maternal separation stress (MSS), a model of ELS, on the expression of five genes involved in endorphin signaling in three brain regions: the hippocampus, hypothalamus and habenula. Our results demonstrate that MSS leads to a significant increase in the mRNA levels of proopiomelanocortin (POMC) and mu opioid receptor - 1 (MOR1) in the hippocampus. In addition, our data reveal that MSS significantly enhances the mRNA levels of kappa opioid receptor - 1 (KOR1) in the hypothalamus. In the habenula, MSS led to a significant reduction in the mRNA levels of proenkephalin (PENK). We simultaneously examined whether the chronic administration of the selective serotonin reuptake inhibitor, fluoxetine, in adulthood was sufficient to reverse any of the effects of MSS on the expression of endorphin system genes. Chronic fluoxetine administration significantly reduced the levels of MOR1 and POMC in the hippocampus, thus essentially reversing the effects of MSS. Fluoxetine also increased the mRNA levels of PENK and reduced the levels of KOR1 in the hippocampus. In the habenula, fluoxetine reduced POMC levels and increased PENK mRNA. In the hypothalamus, fluoxetine administration also significantly increased the mRNA levels of PENK, as it did in the other two brain areas. Prodynorphin (PDYN) mRNA levels were not significantly affected by either MSS or fluoxetine in any of the brain regions examined. Overall, our data reveal new insight into the regulation of the endogenous opioid system by ELS and chronic antidepressant administration in adulthood, which could have important implications for the development and treatment of neuropsychiatric disorders.

**Disclosures: B.D. Sachs:** None. **A. Buncher:** None. **K. Dodson:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.14/MM5

**Topic:** F.04. Stress and the Brain

**Support:** Stanley Medical Research Institute (grants 03-484 and 06T-797).

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FONDECyT

**Title:** Isolation of a potential antipsychotic compound from a Peruvian traditional medicine plant

**Authors: *L. F. TUME**[1], C. GALLO[2], G. POLETTI[2], R. ROJAS[3], M. HURTADO[4], A. J. VAISBERG[1]
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**Abstract:** Background: Schizophrenia is a severe mental disorder that affects approximately 1% of the population. The main symptom is psychosis in which thought and emotions are impaired. Current pharmacological treatments for schizophrenia are partially effective and usually produce side-effects, both factors impacting negatively on patient's adherence to the medication. Since ancient times, Peruvian native communities have recognized behavioral disorders treating them by the use of plant preparations. Peruvian traditional medicine is a potential source of new drugs because of their effectiveness and because they could be acting on different molecular mechanisms compared to the current drugs on the market. Aim: To isolate compounds from a raw plant ethanolic extract (EE) which is active on an animal model of antipsychotic action. Methods: We carried out the isolation based on polarity using preparative chromatography. The compounds were tested in mice treated with MK-801 (N-methyl D-aspartate receptor antagonist). We evaluated hyperactivity in the open field test (OFT)and the prepulse inhibition of startle response (PPI). Cytotoxicity assays were performed on a panel of mammalian cells to determine the GI50 using the sulforhodamine B method. In addition, the EE was tested in binding and functional assays on a panel of receptors altered in mental diseases through the National Institute of Mental Health Psychoactive Drug Screening Program. Results: We obtained a unique chromatographic peak that is active on open field ($p<0.01$) and PPI. The GI50 for this peak is less than the extract in where it was originated. Binding assays performed in the EE showed more than 30% binding to glutamate mGlur5, peripheral benzodiazepine receptor (PBR), serotonin 5-HT2B, histamine H1, and beta 3 receptors. Functional assays revealed that the EE has more than 30% of antagonist activity on GPCR65, GPCR68 and A2A. The EE did not show activity on HERG transport activity. Conclusion: A single peak fraction active in animal models for antipsychotic action has been obtained. The EE has effect on receptors reported to be altered in schizophrenia. Therefore, purification and structure elucidation of the active molecule will help us to the better understand the molecular mechanisms by which is exerting its antipsychotic effect.

**Disclosures: L.F. Tume:** None. **C. Gallo:** None. **G. Poletti:** None. **R. Rojas:** None. **M. Hurtado:** None. **A.J. Vaisberg:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.15/MM6

**Topic:** F.04. Stress and the Brain

**Support:** NSF CAREER award 1253126 to SR

**Title:** Effect of embryonic stress on zebrafish GnRH neurons

**Authors: *G. N. MCHUGH**, S. RAMAKRISHNAN
Biol., Univ. Of Puget Sound, Tacoma, WA

**Abstract:** The Effect of Embryonic Stress Exposure on the GnRH Neurons of Zebrafish (*Danio rerio*)
Stress exposure in zebrafish (*Danio rerio*) has been shown to cause reproductive and developmental impediments. The effects of stress on the reproductive neuroendocrine system in adults and adolescents have been explored, but not the effects on developing embryos. This study investigates the effects of embryonic cortisol (stress) exposure on GnRH neurons in the hypothalamus and pre-optic area (HYP/POA). GnRH neurons in the HYP/POA control the pituitary-gonadal axis (HPG-axis) through the release of reproductive hormones such as luteinizing hormone and follicle stimulating hormone. Changes to the HPG-axis during development can affect fecundity, and sexual reproduction. We wanted to see if early perturbation of this axis via cortisol exposure would have effects on the GnRH neural system. Embryos were collected from transgenic zebrafish with GnRH neurons tagged with a green fluorescent protein (GFP). This allowed for the observation of the developing GnRH neuroendocrine system. These embryos were exposed to chronic doses of cortisol at 5 μM and 10 μM from fertilization until 72 hours post fertilization (hpf). At 72 hpf, GnRH-GFP embryos were anesthetized, mounted and imaged using an inverted epifluorescent microscope at 488nm excitation / 512nm emission. The area and diameter of the HYP/POA-GnRH neurons were measured. Embryos exposed to 10 μM cortisol showed a significant reduction of area by 20% and diameter by 23% in individual GnRH neurons compared to age-matched controls ($p < 0.005$). The lower stress dose of 5 μM did not show any effect on GnRH neuron sizes. Imunohistochemistry was preformed to examine glucocorticoid receptors on GnRH neurons following 10μM cortisol exposure. The number of receptors on cortisol exposed GnRH neurons reduced by almost 50% compared to vehicle treated controls. This is one of the first studies showing that early embryonic stress exposure has direct effects on the developing HYP/POA GnRH neurons involved in the neuroendocrine system.

**Disclosures: G.N. McHugh:** None. **S. Ramakrishnan:** None.

**Poster**

**505. Early-Life Stress: Molecular Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 505.16/MM7

**Topic:** F.04. Stress and the Brain

**Support:** Science Foundation Arizona Bisgrove Fellowship

R01HD079520

R01HD086085

**Title:** Early life stress predicts behavioral problem symptoms, cortisol rhythms, and epigenetic profiles in childhood

**Authors: *C. LEWIS**[1,2], R. S. STYLES[1], I. PIRAS[2], L. D. DOANE[1], M. J. HUENTELMAN[2], K. LEMERY-CHALFANT[1]
[1]Psychology, Arizona State Univ., Tempe, AZ; [2]NeuroGenomics, Translational Genomics Res. Inst., Phoenix, AZ

**Abstract:** Childhood social stressors, such as parental loss, neglect, and abuse, have long been associated with pathogenesis of psychiatric and physical health disorders (McEwen, 1998). Early life stress (ELS) is related to long-lasting alterations in typical and stress-responsive hypothalamic-pituitary-adrenal (HPA) functioning, which is related to psychiatric vulnerability (Gunnar & Quevedo, 2007). A recent review of literature suggests that epigenetic alterations likely mediate ELS-induced HPA dysregulation (Turecki & Meany, 2016). However, less severe childhood environments such as parenting practices also shape HPA function and psychopathology (Kuhlman et al, 2013). We examined whether characteristics of the primary caregiver and parenting practices at 2.5 years of age predicted cortisol diurnal rhythms, behavior problem symptoms, DNA methylation, and RNA expression at 8 years of age. Preliminary analysis included 85 out of 250 twin pairs participating in the longitudinal Arizona Twin Project, 52% female, 32% monozygotic (MZ), 50% European American (Am), 31% Latinx, 9.5% Asian Am, 7% African Am, and 2.4% Native Am (Lemery-Chalfant et al, 2013). ELS was assessed at twin age 2.5 years and is the first principal component of Parenting Daily Hassles, low perceived social support, punitive punishment (Parental Responses to Child Misbehavior), home chaos (Confusion, Hubbub, and Order Scale), CES-D maternal depression, and low maternal emotional availability. Salivary cortisol, buccal cells, and parent report of problem behaviors on the Health and Behavior Questionnaire were collected when twins were 8 years old. Saliva samples were collected in-home three times a day for three consecutive days. Gene methylation and RNA expression was assessed using Infinium HumanMethylation450 BeadChip Kit and RNA sequencing. ELS predicted more conduct disorder [$\beta = .348$, $t(76) = 2.49$, $p = .002$] and

oppositional defiant symptoms [β = .276, $t(76) = 2.49$, $p = .015$]. ELS predicted a flatter evening cortisol slope [β = .256, $t(77) = 2.25$, $p = .027$], but was not associated with morning slope or levels. Additional models examined methylation and RNA expression of HPA axis genes (e.g., glucocorticoid receptor). All analyses controlled for ethnicity, sex, and SES. ELS plays an important role in shaping child development and psychiatric and physical health outcomes. Our results extend this knowledge to less severe environments defined by parenting and characteristics of the primary caregiver. Findings highlight the importance of early childhood environments and elucidate the contributions of early environment to mental health and stress physiology in middle childhood.

**Disclosures: C. Lewis:** None. **R.S. Styles:** None. **I. Piras:** None. **L.D. Doane:** None. **M.J. Huentelman:** None. **K. Lemery-Chalfant:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.01/MM8

**Topic:** F.07. Autonomic Regulation

**Support:** Cyberonics inc. grant

NIH grant R01HL133505

**Title:** Vagus nerve stimulation directly activates limited myelinated afferents but indirectly increases unsynchronized activity in unmyelinated second and higher order sensory neurons in rat nucleus of the solitary tract

**Authors: *E. BEAUMONT**[1], R. P. CAMPBELL[1], M. C. ANDRESEN[2]
[1]Biomed. Sci., ETSU, Johnson City, TN; [2]Physiol. and Pharmacol., Oregon Hlth. & Sci. Univ., Portland, OR

**Abstract: Background:** Vagus nerve stimulation (VNS) is currently used to treat patients with drug resistant epilepsy, depression and, more recently, heart failure. The mild intensities used in chronic VNS suggest that primary visceral afferents and central nervous system activation are involved. Here we determined the neuronal responses of the first vagal receiving neurons within the nucleus of the solitary tract (NTS). **Methods:** NTS neuronal activity was recorded in chloralose anesthetized rats (n=12). Single tungsten electrodes were stereotaxically placed in the caudal medial NTS. A bipolar coil electrode was implanted around the left cervical vagus nerve. High intensity, single or paired shocks established vagal afferent conduction velocity as well as synaptic order (second vs higher). VNS followed clinically styled guidelines for setting bradycardic intensity (BI) at a current intensity which induced a 5% bradycardia. **Results:** Our

chief findings indicate that VNS at BI increased activity in one third of NTS neurons. VNS directly activated only NTS neurons second order to myelinated vagal afferents. Most VNS-induced activity in NTS, however, was unsynchronized to vagal stimuli (spontaneous activity). BI was subthreshold for all direct, vagal C-fiber inputs and yet VNS increased spontaneous but not synchronized spikes in both second and higher order NTS neurons. Overall, NTS neurons that responded to transient changes in blood pressure were similarly activated by BI VNS as pressure-insensitive neurons: 75% monosynaptic vagal A-fibers, 14% monosynaptic vagal C-fibers and 76% vagally polysynaptic neurons. Provocatively, BI VNS was clearly A-fiber selective and yet activated unsynchronized spikes in C-fiber second order neurons ($p<0.05$). Elevation in spontaneous activity was quantitatively much larger than synchronized activity and extended well into the periods of non-stimulation, particularly for NTS neurons receiving higher order inputs. Surprisingly, 33% of polysynaptic NTS neurons responded to 0.5 BI, indicating that large myelinated vagal afferents underlie VNS indirect activation ($p<0.05$). **Conclusions:** This study indicates that VNS directly activates only myelinated vagal afferents to NTS second order neurons without directly activating C-fibers. Conversely, VNS indirectly activated NTS C-fiber second order neurons as well as higher NTS neurons. This indirect activation is likely induced by the recruitment of intra-NTS and/or supra-NTS networks and raise interesting potential for identifying contributions of vagal afferent brain pathways underpinning of therapeutic benefits.

**Disclosures: E. Beaumont:** None. **R.P. Campbell:** None. **M.C. Andresen:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.02/MM9

**Topic:** F.07. Autonomic Regulation

**Support:** JSPS 17K01364

**Title:** A method for the measurement of autonomic control: Quantitative analysis of the properties of cardiovascular dynamics using the scaling exponent computed by mDFA

**Authors: *T. YAZAWA**
Tokyo Metropolitan Univ., Hachioji, Japan

**Abstract:** The beating heart is dynamically controlled by the autonomic nerves. All the organs including the heart is tightly connected through the brain. Fluctuation/variation of the heartbeat represents momently varying inner emotional tension. This psychological variations of the inner world, anxiety for example, is detectable and even quantifiable. Using a long-time electrocardiogram (EKG), we show that we can quantify the state of heart. We recorded EKGs by our own EKG amplifiers. The amplifier has a newly designed electric circuit, which enabled

us to record a stable EKG, i.e,. the amplifier made it possible to capture a perfect EKG where the EKG trace never jump-out from the PC monitor screen. Using this amplifier, we constructed a perfect time series data of approximately 2000 heartbeats without missing a single beat. For the analysis of the EKGs, we used “modified detrended fluctuation analysis (mDFA)” technique, which we have recently developed by our group. The mDFA calculates the scaling exponent (SI, scaling index) from the time series data, i.e., the R-R interval time series data obtained from EKG. Detecting 2000 consecutive peaks, the mDFA can distinguish between a normal and an abnormal heart: a normal healthy heartbeat exhibits an SI of around 1.0, comparable to the fluctuations exemplified as the 1/f spectrum. The heartbeat recorded from subjects who have stress and anxiety exhibited a lower SI. Arrhythmic heartbeats and extra-systolic heartbeats both also exhibited a low SI ~0.7, for example. We propose that the mDFA technique is a useful computation method for checking the cardiac control condition which reflects the state of mind as well as the state of heart functioning.

**Disclosures: T. Yazawa:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.03/MM10

**Topic:** F.07. Autonomic Regulation

**Support:** RFBR grant 16-04-00538

RFBR grant 17-04-00349

**Title:** Development of NO-ergic synaptic transmission in sympathetic ganglia

**Authors: *P. M. MASLIUKOV**, K. MOISEEV
Normal Physiol., Yaroslavl State Med. Univ., Yaroslavl, Russian Federation

**Abstract:** NO is generated by the enzyme nitric oxide synthase (NOS) and acts as a neuromodulator in the sensory and autonomic neurons A large number of adult mammalian sympathetic preganglionic neurons express NOS. However, there are only few works concerning the development of NO-mediated synaptic transmission in the sympathetic ganglia. The aim of this study was to identify expression of NOS in sympathetic preganglionic neurons and effects of NO on synaptic transmission in sympathetic ganglia during the development.
Experiments were performed on rats of different ages (newborn, 10-day-old, 20-day-old, 30-day-old, 180-day-old, 3-year-old) using immunohistochemistry, electrophysiology and western-blotting in accordance with the national and international principles of laboratory animal care. The results showed that in all age groups NOS-immunoreactive (IR) neurons were absent in

sympathetic ganglia. In the spinal cord, the largest number of NOS-IR sympathetic preganglionic neurons was located in the nucleus intermediolateralis thoracolumbalis pars principalis (nucl.ILp). In newborns, a large portion of NOS-IR neurons colocolized calbindin, calretinin and cocaine- amphetamine-regulated transcript (CART). During the first month of life, the proportion of NOS-IR neurons decreased significantly, while the number of neurons containing choline acetyltransferase increased. In newborns, all preganglionic neurons were NOS-IR, while in one-month-old rats 30-35% of preganglionic sympathetic spinal neurons were NOS-immunonegative. Decreasing in the expression of NOS in the spinal cord in the first month of life was further confirmed by western blotting. Evoked synaptic potentials in the superior cervical sympathetic ganglion were inhibited with NO donor sodium nitroprusside and augmented by the NO synthase inhibitor L-NAME from the moment of birth. We did not observe any difference on the morphological and electrophysiological properties of NOS-IR neurons between adult and old rats.
Thus, in early postnatal ontogenesis, there is an age-related change in NO-ergic sympathetic transmission with in a decrease in the number of sympathetic preganglionic neurons expressing NOS in the early development. NO inhibits synaptic transmission in sympathetic ganglia in young and old rats.

**Disclosures: P.M. Masliukov:** None. **K. Moiseev:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.04/MM11

**Topic:** F.07. Autonomic Regulation

**Support:** NIH R15HL127739

**Title:** Y1 and Y5 receptor localization and function in the guinea pig cardiac plexus

**Authors: F. M. TIERNEY**[1], S. E. ALLEN[1], A. M. GINSBURG[1], *J. C. HARDWICK[2]
[1]Biol., [2]Ithaca Col., Ithaca, NY

**Abstract:** Chronic heart disease leads to imbalances within the autonomic nervous system, often resulting in an upregulation of sympathetic output with a corresponding decrease in central parasympathetic activity. In addition to the increased release of norepinephrine from sympathetic fibers, there is also an elevation in the release of the neuropeptide, NPY, from sympathetic fibers. These sympathetic efferents also innervate the intrinsic cardiac nervous system. Parasympathetic neurons of the cardiac plexus respond to NPY with a hyperpolarization and a decrease in the duration of the afterhyperpolarization of the action potential. This study examined the expression of specific NPY receptor subtypes in intracardiac neurons of the guinea

pig intrinsic cardiac plexus. In addition, we characterized the role of receptor subtypes in mediating the changes in action potential properties. Preliminary analysis of mRNA for NPY receptors demonstrated that both Y1 and Y5 receptors are expressed in the cardiac plexus and within atrial muscle tissue. Immunohistochemical studies show significant expression of Y1R in cardiac neurons, although not all neurons express the Y1 receptors. Y5R staining was not as prominent in neurons as the Y1R. Intracellular voltage recordings from cardiac neurons were performed on whole mount preparations superfused with either 100 nM NPY, 100 nM D-Arg-NPY (Y1-specific) agonist, or 100 nM BWX-46 (Y5-specific agonist). A two minute perfusion with NPY resulted in a ~25% reduction in the t1/2 (time to reach 50% of original resting membrane potential) of the afterhyperpolarization. Perfusion with the Y1 agonist produced a similar response. Perfusion with the Y5 agonist was less potent (~15% reduction with a shorter duration of action), suggesting that expression/function of the Y5R is reduced in neurons, relative to the Y1R. Addition of the Y1R-specific antagonist, BVD 10 (1 uM) to the perfusion solutions completely inhibited the response to D-Arg-NPY, without altering the response to the Y5 agonist. The response to NPY in the presence of the Y1 antagonist was smaller with a shorter duration, similar to the Y5 agonist. Taken together, these studies suggest that the Y1R is the predominant NPY receptor on intracardiac neurons, but there is also evidence for Y5R expression. Both of these receptors appear to induce alterations in ionic currents underlying the action potential and future studies will explore the ionic mechanisms of these receptors in more detail and as well as how their expression and function is affected by chronic heart disease.

**Disclosures:** **F.M. Tierney:** None. **S.E. Allen:** None. **A.M. Ginsburg:** None. **J.C. Hardwick:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.05/MM12

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant OT2OD023867

**Title:** Brainstem circuitry supporting auricular vagus nerve stimulation effects on cardiovagal outflow in rats

**Authors:** C. S. HUBBARD[1], V. NAPADOW[2], R. SCLOCCO[3], R. BARBIERI[4], R. G. GARCIA[5], ***I. AY**[6]
[2]Martinos Ctr. for Biomed. Imaging, [1]Massachusetts Gen. Hosp., Charlestown, MA; [3]Athinoula A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hospital, Harvard Med. Sc, Charlestown, MA; [4]Dept Anesthes Critical Care, Massachusetts Gen Hosp, Boston, MA;

[5]Martinos Ctr. For Biomed. Imaging, Charlestown, MA; [6]Dept Radiol, Mass Gen. Hosp., Charlestown, MA

**Abstract: Introduction:** The vagus nerve plays an important role in the regulation of cardiovascular function and vagus nerve stimulation (VNS) in patients with cardiovascular disease improves prognosis. VNS has negative chronotropic and dromotropic effects, reduces baroreflex sensitivity, and decreases circulating plasma catecholamine levels. In animal models of myocardial infarction, VNS prevents ventricular fibrillation and sudden cardiac death. Despite these promising findings, morbidity associated with invasive VNS has limited its clinical application. Thus, the mapping of alternative non-invasive pathways for vagal modulation is of critical relevance. An alternative, non-invasive method of VNS is stimulation of the auricular branch of the vagus nerve (ABVN) in the external ear. However, the neural pathway connecting ABVN afference with cardiovascular outcomes is not well understood. In this study, we aim to functionally map the ABVN – brainstem – cardiovagal outflow pathway in rats.
**Methods:** Healthy adult male and female Wistar rats were used. We evaluated cardiovagal efference by recording ECG and cervical vagus nerve activity in response to ABVN stimulation. ECG was used for heart rate variability (HRV) analysis which is the most effective and widely used method to assess autonomic modulation of cardiac reflex function. We calculated power in high frequency band (HF-HRV) that reflects cardiac parasympathetic nerve activity and power in low frequency band (LF-HRV) that has a dominant sympathetic component. To characterize brainstem circuitry activated by ABVN stimulation, we stereotaxically injected lidocaine to inhibit neuronal activity in selective nuclei including nuclei tractus solitarii (NTS). At the end of the stimulation-recording period, brains were obtained for c-Fos immunohistochemistry as a surrogate marker for neuronal activation.
**Results:** We recorded ECG and cervical vagus nerve activity before, during, and after ABVN stimulation in control (n=5) rats and animals that received bilateral lidocaine injection (4%, 0.1 μl per site; n=5) into the NTS. HRV analysis showed that ABVN stimulation significantly increased HF-HRV power and decreased LF-HRV/HF-HRV ratio ($p<0.05$). The effect of ABVN stimulation on these parameters was abolished in rats that underwent NTS blockade. Preliminary analysis of cervical vagus nerve activity suggests that rapid biphasic response to ABVN stimulation was absent in animals with NTS blockade.
**Conclusion:** ABVN stimulation increased cardiovagal outflow via the NTS. Involvement of other nuclei and the contribution of specific neurotransmitter systems will be evaluated further.

**Disclosures: C.S. Hubbard:** None. **V. Napadow:** None. **R. Sclocco:** None. **R. Barbieri:** None. **R.G. Garcia:** None. **I. Ay:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.06/MM13

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant R00 DC012803

**Title:** Breathing and the amygdala: Potential implications for SUDEP

**Authors:** W. P. NOBIS[1], ***C. ZELANO**[2], J. TEMPLER[2], G. LANE[2], G. ZHOU[2], S. SCHUELE[2], *C. ZELANO[2], *C. ZELANO[2]
[1]NEUROLOGY, [2]Northwestern Univ., Chicago, IL

**Abstract:** Sudden unexplained death in epilepsy (SUDEP) is the most frequent cause of death in epilepsy patients. Accumulating evidence indicates that SUDEP may involve impaired breathing and apnea during and after seizures. However there are a number of additional known pathologic features of SUDEP including ictal arrhythmias, ictal or postictal central apnea and autonomic dysregulation. The variety of pathological features combined with the rareness of the disease have left the underlying neural mechanisms of SUDEP poorly understood. Brainstem structures have been implicated in some models of SUDEP, but higher order control of these structures by seizures is unknown. The extended amygdala, comprising chiefly of the central amygdala and the bed nucleus of the stria terminalis, is a part of the central autonomic network that is interconnected between higher order cortical areas, brainstem, and hypothalamic networks raising the possibility that it could be the missing link in the mediation of SUDEP. The central amygdala is activated by seizures, and its activation can have powerful effects on heart rate, blood pressure and respiratory function. Furthermore, extended amygdala projections reach areas that are important for control of cardiorespiratory function including the nucleus of the solitary tract and the ventrolateral medulla. Recent intracranial EEG data from several groups have shown that electrical stimulation of the human amygdala induces apnea, and recent local field potential recordings have demonstrated that neural oscillations in the amygdala become synchronized during natural inhalation. Taken together, these data suggest a role for the amygdala in controlling respiration. In this study, we will show data from five additional epilepsy patients confirming that electrical stimulation of the human amygdala induces apnea. Preliminary data suggest that this stimulation-induced apnea can be prevented in two ways. First, if the patient is instructed to take a breath after the apnea has begun, they are able to do so, suggesting it can be overcome with preserved consciousness. Second, if stimulation is administered during mouth breathing (as opposed to nose breathing), no apnea occurs. Our data support the hypothesis that the amygdala may play a role in SUDEP, and also provide evidence for two techniques that can overcome or prevent amygdala-related apnea.

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**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.07/MM14

**Topic:** F.07. Autonomic Regulation

**Support:** NIH grant HL-72006

**Title:** Direct projections from orexin neurons to pre-sympathetic neurons in the paraventricular nucleus of the hypothalamus

**Authors: *O. DERGACHEVA**, D. MENDELOWITZ
Pharmacol. & Physiol., GW Univ., Washington, DC

**Abstract:** Orexin neurons are generally thought to be sympathoexcitatory; however, the functional connectivity between orexin neurons and the bulbospinal pre-sympathetic neurons (PSNs) in the paraventricular nucleus of the hypothalamus (PVN), has not been established. To test the hypothesis that orexin neurons project directly to PSNs in the PVN, channelrhodopsin-2 (ChR2) was selectively expressed in orexin neurons to enable photoactivation of ChR2-expressing fibers while examining evoked postsynaptic currents in PSNs in rat hypothalamic slices. Selective photoactivation of orexin fibers elicited short-latency postsynaptic currents in PSNs. These light-triggered responses were heterogeneous, with a majority being excitatory glutamatergic responses (59%), and a minority of inhibitory GABAergic (35%) and mixed glutamatergic and GABAergic currents (6%). Glutamatergic, but not GABAergic, postsynaptic currents were diminished by application of the orexin receptor antagonist almorexant indicating orexin release facilitates glutamatergic neurotransmission in this pathway. This work identifies a neuronal circuit by which orexin neurons likely exert sympathoexcitatory control of cardiovascular function.

**Disclosures: O. Dergacheva:** None. **D. Mendelowitz:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.08/MM15

**Topic:** F.07. Autonomic Regulation

**Support:** NSF 1257162

**Title:** Establishing meadow voles as a model system for studying cardiac function and social behavior

**Authors: *J. D. CHRISTENSEN**[1,2], A. K. BEERY[2]
[1]Univ. of Massachusetts, Amherst, MA; [2]Biol., Smith Col., Northampton, MA

**Abstract:** In recent decades, multiple vole species have provided valuable insights into different social behaviors. Meadow voles exhibit changes in their social behavior across seasons. Female meadow voles are highly territorial and aggressive toward other females in the summer months, but in the short days of winter, they form selective, communal groups. For this study, female meadow voles were pair housed in either short or long photoperiods. Individuals were implanted with cardiac telemetry transmitters and baseline cardiac parameters were measured. Following collection of baseline data, specific autonomic nervous system signaling pathways were suppressed using atenolol, atropine, or a combination of the two, and compared to a saline control injection. All individuals underwent all treatments, which were counterbalanced with 48 hours between treatments. Atenolol is a beta-receptor blocker that has been shown to increase heart rate by antagonizing the cardiac response to circulating epinephrine and norepinephrine. Atropine is a muscarinic acetylcholine receptor blocker that decreases heart rate variability and the phenomena of respiratory sinus arrhythmia. Prior studies have characterized cardiac function in prairie voles—a close relative of the meadow vole; female prairie voles were included in this study to allow direct comparisons. Meadow vole heart rate and heart rate variability were not significantly different from those of prairie voles. Meadow voles responded as expected to pharmacological suppression of the autonomic nervous system, and effects of these drugs did not differ between the species. Additional data will be presented on photoperiodic variation within meadow voles. Characterization of meadow vole cardiac physiology will allow for future studies of the influence the autonomic system has on behavior and vice versa.

**Disclosures: J.D. Christensen:** None. **A.K. Beery:** A. Employment/Salary (full or part-time):; Smith College. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); National Science Foundation.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.09/MM16

**Topic:** F.07. Autonomic Regulation

**Support:** General Program of National Natural Foundation of China (No. 81273828)

**Title:** Role of muscarinic acetylcholine receptor 2 in anti-myocardial ischemia effect by acupuncture

**Authors: *S. CHEN**, C. DUANMU, J. WANG, L. QIAO, J. LIU, J. ZHANG
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**Abstract:** Ischemic heart diseases are common malady leading to serious impacts on people's health in developed as well as developing countries. Previous studies show that acupuncture produces positive therapeutic effects on these diseases. Given the fact that acute myocardial ischemia (AMI) is usually concomitant with the increase of the sympathetic nerve activities but decrease of the vagal nerve activities, we hypothesized that acupuncture reduces MI via enhancement of the vagal tones. This work was carried out on the wild type (WT) and gene knockout (KO) muscarinic acetylcholine receptor M2 (M2AChR) mice. The MI model was developed by isoproterenol administration i.p. Electroacupuncture (EA) stimulation (0.5mA, 2Hz) was applied at "Neiguan" acupoint (PC6) for 20 minutes. Electrocardiogram (ECG) was recorded for the evaluation of the MI condition as well as the analysis of heart rate variability (HRV) via the root mean square of successive differences (RMSSD), high frequency (HF) and the ratio of low frequency (LF) verus HF and so forth. Further, by means of the biochemical, immunohistochemical and molecular biological methods, we evaluated the changes of relevant cardiac enzymes in serum, and the expressions of the M2AChR and the downstream molecules like bcl-2 and caspase3 in the ventricular myocardium. We found that 1. KO mice demonstrated higher heart beats than WT mice particularly in MI-1d period. During MI induction, the ST-segment and the J-point of ECG elevated or lowered notably in both WT and KO mice. Concurrently, the heart rate accelerated, the RMSSD and HF decreased whereas the ratio of LF/HF increased significantly. 2. EA could reverse the abovementioned changes. In comparison with the WT mice, EA led to no much effect on KO mice evaluated with RMSSD. Atropine, the M2 receptor antagonist, blocked the EA effect of elevating RMSSD and reducing the ration of LF/HF. 3. MI resulted in significant increase of serum LDH and CK-MB in both content and activity. After EA treatment, these increases were reduced. 4. EA upregulated the expressions of M2 and its intracellular downstream molecule bcl-2 reduced by MI but downregulated the expressions of caspase3 raised by MI. The evidence indicates that acupuncture achieves the effect of MI reduction through the M2AChR and bcl-2/caspase3 signaling transduction pathway. Our study provides new data for the elucidation of the molecular mechanism of acupuncture on MI and thereby holds promise for the management of cardiovascular diseases in clinic.

**Disclosures: S. Chen:** None. **C. Duanmu:** None. **J. Wang:** None. **L. Qiao:** None. **J. Liu:** None. **J. Zhang:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.10/MM17

**Topic:** F.07. Autonomic Regulation

**Title:** Exercise training normalizes excitability of presympathetic neurons by increasing GABAergic transmission in heart failure rats

**Authors: Y. SHEN**[1], S. LEE[1], S. HAN[2], *P. RYU[1]
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**Abstract:** Sympathetic hyper-activation is a hallmark of heart failure (HF). Recent studies showed that exercise training (ExT) decreases peripheral sympathetic nerve activity in HF patients. However, underlying mechanisms of such effects are not well understood. In this study, we examined the changes in the hypothalamic presympathetic neurons in the HF rats after a 3-week period ExT. The rat model of HF was prepared by ligation of left descending coronary artery. At 3-4 weeks after the surgery, the animals were exercised on a motor-driven treadmill for 3 weeks. At 8$^{th}$ week following the surgery, the electrical activity of the paraventricular nucleus neurons projecting to the rostral ventrolateral medulla (PVN-RVLM) was recorded by slice patch clamp technique combined with retrograde tracing. We also collected electrocardiogram data for heart rate variability (HRV) analysis. ExT induced a reduction in the firing rate of PVN-RVLM neurons in HF rats (3.40 vs. 1.98 Hz) with an increase in the frequency of IPSCs (1.13 vs. 3.14 Hz) without affecting EPSC. Replacement of $Ca^{2+}$ with $Mg^{2+}$ in recording solution reduced miniature IPSC frequency more in HF-ExT than in HF group (40.4 vs. 71.4%). GABA-A receptor blocker (bicuculline, 20 μM) increased the firing rate more in HF-ExT than in HF rats (10.3 vs. 93.0%). In addition, the input resistance (752 vs. 1025 Mohm) and the peak of after hyperpolarization (-22 vs. -26 mV) in PVN-RVLM neurons were larger in HF-ExT rats than HF rats. ExT also reversed the reduced circadian fluctuations in heart rate and the sympatho-vagal activity in HF rats. Collectively, the results indicate that ExT normalizes the hypothalamic pre-sympathetic hyper-activation and blunted circadian rhythm in sympatho-vagal balance in HF rats. These are largely due to ExT-induced increase in GABA release. Our findings newly provide a synaptic mechanism of ExT-induced beneficial effect in HF patients.
**Keywords:** slice patch clamp; firing rate; heart rate variability

**Disclosures:** **Y. Shen:** None. **S. Lee:** None. **S. Han:** None. **P. Ryu:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.11/MM18

**Topic:** F.07. Autonomic Regulation

**Support:** CONACyT Grant 252702

**Title:** Effect of sodium hydrosulfide on tachycardic responses induced by stimulation of the preganglionic sympathetic outflow in pithed rat

**Authors: *S. HUERTA**, S. V. CASTILLO-SANTIAGO, M. E. CHACON-BECERRIL, J. A. TORRES-PÉREZ, A. SÁNCHEZ-LÓPEZ, D. CENTURION
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**Abstract:** Hydrogen sulfide ($H_2S$) is a gasotransmitter that, at physiological concentrations, mediates complex responses in the cardiovascular system. Recently it has been shown that $H_2S$ produces negative chronotropic and inotropic responses in isolated heart. Also, in anesthetized rats, it has been observed that sodium hydrosulfide (NaHS) induces bradycardia although the mechanisms remain elusive. On this basis, the present study was designed to explore the potential capability of NaHS to inhibit the cardiac sympathetic outflow in pithed rat. For this purpose, 72 male Wistar rats (300-350 g) were used. Animals were anesthetized with isoflurane (3%), the trachea was cannulated for artificial ventilation and the rats were pithed by inserting a stainless-steel rod through the orbit and foramen magnum into the vertebral foramen which was later replaced by an electrode enamelled except for 1 cm length 7 cm from the tip to stimulate the cardiac sympathetic outflow (C7-T1). Catheters were placed in: the left and right femoral veins for drugs administration and the left carotid artery to record heart rate and blood pressure. Animals were initially divided into 3 groups: (1) cardiac sympathetic outflow stimulation; (2) i.v. bolus of exogenous noradrenaline; and 3) i.v. bolus of isoproterenol. Those groups were then subdivided into 4 groups that received a continuous infusion of (1) nothing (control group); (2) PBS (vehicle); (3) NaHS 310 μg/kg min; and (4) NaHS 560 μg/kg min. We observed that tachycardic responses induced by cardiac sympathetic outflow stimulation were significantly diminished in a dose-dependent manner by i.v. continuous infusion of NaHS. Nevertheless, continuous infusion of NaHS failed to modify on tachycardic responses induced by i.v. bolus of noradrenaline or isoproterenol. Thus, we concluded that NaHS inhibits the tachycardic responses through a pre-junctional mechanism and did not interact directly with post-junctional receptors.
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**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.12/MM19

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant ZIA MH002928-01

**Title:** The role of periaqueductal gray (PAG) lesions on pain processing and cardiovascular regulation

**Authors: *S. NAIR**, P. BROWNING, E. A. MURRAY, B. B. AVERBECK
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**Abstract:** The periaqueductal gray (PAG) is located in the midbrain, immediately surrounding the cerebral aqueduct. It plays an important role in mediating defensive behaviors and it influences functions including pain processing, fear and anxiety, cardiovascular control, vocalization, and lordosis. Although there has been considerable work on the PAG in rodents, there is minimal work on this structure in monkeys. Some functions attributed to the PAG, including intra-specific threat processing, may differ among species. Therefore we have examined the effects of ibotenic acid lesions of the PAG in rhesus monkeys (*Macaca mulatta*) on both pain processing and cardiovascular control. We examined both of these functions through four separate assessments each, two pre-operative and two-post-operative. Pain was measured through the use of a von Frey (VF) filament-based nociception assay and vital signs were obtained using standard procedures. Our preliminary results indicate no significant difference between the change in pre-operative and post-operative VF measurements or vital signs when comparing monkeys with PAG lesions (n = 4) and sham-operated controls (n = 4). Ongoing work includes evaluation of social and nonsocial defensive responses.

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**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.13/MM20

**Topic:** F.07. Autonomic Regulation

**Title:** Moderate intensity exercise improves heart rate variability in obese adults with type 2 diabetes

**Authors: *R. K. GOIT**
Nepalgunj Med. Col., Banke, Nepal

**Abstract:** The aim of this study was to determine the effect of moderate aerobic exercise on heart rate variability (HRV) in obese adults with type 2 diabetes. 41 obese adults with type 2 diabetes participated in this study. Anthropometric and metabolic parameters were measured, and resting electrocardiogram (ECG) for the HRV analysis at spontaneous respiration was recorded for 5 min in supine position before and after six months of supervised aerobic training given thrice-a-week. The mean age, body mass index (BMI), and duration of diabetes of the study population were 44.1 ± 4.5 years, 30.94 ± 1.36 kg/$m^2$, and 16.3 ± 2.7 years, respectively. In time domain variables, standard deviation of all RR intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD) and percentage of consecutive RR intervals that differ by more than 50 ms (pNN50) were significantly increased after exercise. In frequency domain variables, high frequency (HF) ($ms^2$) and HF (nu) were significantly increased while low frequency (LF) ($ms^2$) were significantly decreased after exercise. But LF (nu) and LF/HF ratio were unaffected after exercise. These data suggest that thrice-a-week moderate intensity aerobic exercise for six months improves cardiac rhythm regulation as measured by HRV in obese adults with type 2 diabetes.

**Disclosures: R.K. Goit:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.14/MM21

**Topic:** F.07. Autonomic Regulation

**Support:** FAPESP

CNPq

PROPE/FUNDUNESP.

**Title:** Inhibition of catalase reduces arterial pressure and renal sympathetic nerve activity in hypertensive rats

**Authors: *M. R. LAUAR**[1], L. T. TOTOLA[2], T. S. MOREIRA[2], D. S. A. COLOMBARI[1], L. A. DE LUCA JR[1], P. M. DE PAULA[1], E. COLOMBARI[1], C. A. F. ANDRADE[1], J. V. MENANI[1]

[1]Dept Physiol. and Pathol., Dent. School, UNESP, Araraquara, Brazil; [2]Dept of Physiol. and Biophysics, Inst. of Biomed. Sci., Univ. of Sao Paulo, USP, Sao Paulo, Brazil

**Abstract:** The 2-kidneys, 1-clip (2K1C) hypertension is characterized by increased renin-angiotensin system (RAS) and sympathetic activity. In rats with 2K1C hypertension, chronic subcutaneous (sc) administration of the catalase inhibitor 3-amino-1,2,4-triazol (ATZ) reduces mean arterial pressure (MAP) and improves autonomic modulation. In the present study, we analyzed the changes in renal and splanchnic sympathetic nerve activity in 2K1C hypertensive rats treated with sc injection of ATZ. Male Holtzman rats (initial weight 150-180 g, n=4-6/group) received a silver clip around the left renal artery to generate 2K1C hypertension. Six weeks after the surgery, MAP and renal (rSNA) and splanchnic (sSNA) sympathetic nerve activity were recorded in urethane-anesthetized and artificially-ventilated rats that received an injection of ATZ (300 mg/kg of body weight) sc. The sc injection of ATZ in 2K1C hypertensive rats reduced MAP (160 ± 13 mmHg 1 h after ATZ, vs. control: 180 ± 13 mmHg pre-ATZ) and rSNA (-52 ± 10% 1 h after ATZ), without significantly changing the sSNA (-8 ± 16%). The present results suggest that increasing the availability of endogenous $H_2O_2$ with the injection of ATZ produces anti-hypertensive effects associated with decrease in renal sympathetic nerve activity.

**Disclosures: M.R. Lauar:** None. **L.T. Totola:** None. **T.S. Moreira:** None. **D.S.A. Colombari:** None. **L.A. De Luca Jr:** None. **P.M. De Paula:** None. **E. Colombari:** None. **C.A.F. Andrade:** None. **J.V. Menani:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.15/MM22

**Topic:** F.07. Autonomic Regulation

**Support:** NIH NINDS R01NS099076

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NIH NINDS R01NS085426

DoD/CDMRP W81XWH-14-1-0605

**Title:** The development of cardiovascular dysfunction in a rat spinal cord crush model and responses to pharmacological interventions of serotonin and dopamine receptors

**Authors: *C. TRUEBLOOD**, I. IREDIA, V. J. TOM, S. HOU
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

**Abstract:** Selection of a proper spinal cord injury (SCI) animal model that is conducive to study therapeutic effects of cell transplantation is imperative for research in cardiovascular functional recovery. We recently found that neural stem cells grafted into the lesion of crushed spinal cord achieved better survival and integration than other dura-opened injuries. However, it is unknown whether cardiovascular dysfunction develops in this model. Disordered hemodynamics following SCI is mainly attributed to the interruption of supraspinal pathways. Given the preservation of neurotransmitter receptors in the lower cord, e.g., those for serotonin (5-HT) or dopamine (DA), they could be potential targets for drug treatment to restore autonomic function. Accordingly, the purpose of this study was to determine hemodynamic consequences of a crushed SCI, and to define the effects of 5-HT or DA receptor agonists on cardiovascular performance. Adult rats underwent complete spinal cord crush at the $4^{th}$ thoracic level. Using a radio-telemetric system, we recorded multiple hemodynamic parameters prior to or 2 and 4 weeks after injury, including resting mean arterial pressure (MAP) and heart rate (HR), as well as spontaneous or colorectal distension (CRD)-induced autonomic dysreflexia (AD), evidenced by simultaneous hypertension and bradycardia. This was followed by drug delivery targeting 5-HT and DA receptors. The results showed that resting HR was dramatically increased whereas MAP did not change compared to pre-injury. Spontaneous AD occurred after injury, without distinction in events at different time points. Yet, developed CRD-induced AD revealed a significant increase in MAP change and decrease in HR change over time. In the chronic stage of SCI, subcutaneous administration of apomorphine (a non-selective DA receptor agonist, 10-300 μg/kg) or 8-OH-DPAT (a 5-$HT_{1A}$ receptor agonist, 5-100 μg/kg) did not affect resting hemodynamics. In contrast, a 5-$HT_{2A}$ receptor agonist DOI (5-100 μg/kg) remarkably increased resting MAP levels with dose-dependent effects. During CRD, administering DOI (20 μg/kg) did not eliminate or alleviate episodic hypertension. Additionally, intrathecal injection of DOI (1-20 μg/kg) in urethane-anesthetized SCI rats elicited a cumulative response of increased resting MAP and decreased HR, indicating the effects at least partially via the central mechanism. Histological analysis confirmed lesion completeness in most cases using serotonergic axons as an indicator. Thus, the crushed SCI is sufficient to induce cardiovascular abnormalities and this model responds sensitively to pharmacological stimulation of 5-$HT_{2A}$ receptors.

**Disclosures: C. Trueblood:** None. **I. Iredia:** None. **V.J. Tom:** None. **S. Hou:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.16/NN1

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant HL133862

**Title:** Monosynaptic excitatory projection from PVN oxytocin neurons to the LC

**Authors: *X. WANG**[1], D. S. MENDELOWITZ[2]
[1]Pharmacol. and Physiol., [2]George Washington Univ., Washington, DC

**Abstract:** The paraventricular nucleus of the hypothalamus (PVN) and the locus coeruleus (LC) are critical in controlling autonomic function under normal conditions and regulating cardiovascular activity in response to stressful challenges. The PVN is a heterogeneous nucleus, including the vasopressin neurons and oxytocin (OXT) neurons. It has been reported that oxytocin released from PVN oxytocin neurons can reduce anxiety and stress. Neurons in the locus coeruleus (LC) innervate extensive areas of the brain and the spinal cord and are most active in wakefulness. Systemic application of oxytocin may increase social interaction and decrease anxiety and stress reactions by decreasing noradrenergic release in the locus coeruleus. This study is to examine whether oxytocin neurons in the PVN directly modulate the LC neuron activity or not. To selectively expression and stimulation of PVN oxytocin neurons we applied viral transfection approach. Two viral vectors in combination with the Cre-Lox recombination system were used. In this system one viral vector expresses Cre recombinase under the specific oxytocin promotor. The second vector expresses ChR2 (H134R). This is a Cre-dependent vector that has silencing double-floxed inverse open reading frames which insures expression is only initiated in oxytocin neurons that selectively express Cre. Whole cell patch clamp technique was used to recording stimulation evoked postsynaptic events in the LC neurons. Biocytin (0.05%) was added in the patch solution to further identify the neurons in the LC using immunohistochemistry staining. Ontogenetic stimulation of ChR2 expressing PVN oxytocin-cre-fibers evoked excitatory inward currents in LC neurons with an average of amplitude of -65.4 ± 4 pA . This evoked excitatory currents was blocked by the glutamatergic receptor antagonists AP-5 (50 μM) and CNQX (μM). Further work will examine the roles, if any, co-release of oxytocin.

**Disclosures: X. Wang:** None. **D.S. Mendelowitz:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.17/NN2

**Topic:** F.07. Autonomic Regulation

**Support:** Conacyt 252702

**Title:** Analysis of the vasopressor responses induced by sympathetic stimulation or several adrenergic agonists in pithed rats treated with high-fat diet

**Authors: *A. SACHEZ-LOPEZ**, M. E. BECERRIL-CHACON, E. J. GUTIÉRREZ-LARA, D. CENTURIÓN
Farmacobiología, Cinvestav-Coapa, Mexico, Mexico

**Abstract:** Obesity is a risk factor for the development of cardiovascular diseases. The extent to which obesity affect the cardiovascular function in pithed rats remains unknown. Thus, the aim of this study was to determine the effect of high-fat diet on the vasopressor responses induced by sympathetic stimulation. This experimental model allows evaluating the cardiovascular responses without the influence of the central nervous system. For this purpose, 12 animals were divided into two groups. The first group (n=6) was treated with normal diet and the second group (n=12) was treated with high-fat diet with lard 30% during 12 weeks. Next, body weight, blood triglyceride levels as well as blood glucose and plasma insulin were determined before postprandial glucose. In both groups the blood glucose and plasma insulin were determined after administration of glucose (1 g $Kg^{-1}$, p.o.) at 5-120 min. Then, rats were: (1) anaesthetized with isoflurane; (2) pithed with a stainless steel road; (3) assisted with artificial ventilation; and (4) cannulated for i.v. administration of several drugs. The vasopressor effects to sympathetic stimulation or i.v. administration of noradrenaline (1-10 mg $Kg^{-1}$), methoxamine (0.03-10 μg $Kg^{-1}$) and UK 14,304 (0.56-18 μg $Kg^{-1}$) were determined. High-fat diet produced increases in body weight without significant changes in basal blood glucose, basal plasma insulin or HOMA-index or blood triglycerides. However, high-fat diet (HFD) significantly decreased glucose tolerance after administration of 1 g $Kg^{-1}$ glucose (p.o.) while plasma insulin levels remained unchanged. Furthermore, sympathetic stimulation or i.v. administration of noradrenaline, methoxamine or UK 14,304 elicited dose-dependent vasopressor responses in either animals treated with normal diet or HFD. The responses to sympathetic stimulation remained unaffected by HFD. In marked contrast, the vasopressor responses were significantly increased by HFD. The above results suggest that high-fat diet significantly increased the functionality of alpha1 and alpha2 adrenoceptors in systemic.

**Disclosures: A. Sachez-Lopez:** None. **M.E. Becerril-Chacon:** None. **E.J. Gutiérrez-Lara:** None. **D. Centurión:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.18/NN3

**Topic:** F.07. Autonomic Regulation

**Title:** Alpha and beta adrenergic receptors increase the serotonin-induced vascular smooth muscle contraction through $Ca^{2+}$ regulation

**Authors: *D. M. MEJÍA**[1], P. SEGURA MEDINA[2], V. CARBAJAL SALINAS[2], M. VARGAS BECERRA[1], E. TORREJÓN GONZÁLEZ[1], P. CAMPOS BEDOLLA[1]
[1]Inst. Mexicano del Seguro Social, Ciudad de México, Mexico; [2]Inst. Nacional de Enfermedades Respiratorias, Mexico, Mexico

**Abstract: Background**: Role of serotoninergic and adrenergic systems has been widely studied in the vascular smooth muscle (VSM) tone and cardiovascular physiology. Serotonin (5-hydroxytryptamine) is one of the main vasoconstrictors in arteries and veins trough the 5-$HT_{2A}$ receptor. In the same way, alpha- and beta- adrenergic receptors (a- and b-AR) are principal therapeutic targets in a lot of cardiovascular pathologies. Previously, in other studies we have found that 5-$HT_{2A}$ receptor just contribute partially in aorta contraction. For this reason, we proposed that other signaling pathways could be participating. Due to the importance of $Ca^{2+}$ intracellular concentration ($[Ca^{2+}]i$) for an adequate VSM contraction, we evaluated the adrenergic system role in the serotonin-induced aorta contraction and the $[Ca^{2+}]i$ by simultaneous measurements *in vitro* model. **Material and methods**: Thoracic aorta rings were obtained from male Hartley guinea pigs (400-600 g) and stimulated by non-cumulative 5-HT concentrations (0.1 to 100 μM). The role of 5-$HT_{2A}$ receptor was evaluated with the antagonist ketanserin (0.01 μM, KT). In addition, we used α- and β- AR agonist and antagonists on 5-HT-contraction by *in vitro* system. In another set of experiments, we evaluated simultaneous measurements of $[Ca^{2+}]i$ and vascular contraction. Contraction responses were expressed respect to 80 mM KCl maximal contractile activity by mean±SEM. **Results**: All 5-HT concentration produced sustained contraction on aorta rings, and it is concentration-dependent response. The maximal contractile activity by 100 μM of 5-HT (56.68±1.4%) was reduced by KT (33.01±1.27%) in 41.76% of the response. a- and b- AR antagonists reduced significantly 100 μM 5-HT contraction. Prazosin (a-AR antagonist) decreased highly significantly by 50.66% 5-HT contraction ($p<0.0001$). And propranolol, (b-AR antagonist) reduced 54.49% ($p<0.0001$). Consistently with another studies, we found that α-AR agonist, phenylephrine, induced the maximal contraction response (94.09±3.19%) on aorta, while isoproterenol (b-AR agonist) scarcely induced 3.39±0.8% of aorta contraction. $[Ca^{2+}]i$ was 100% decreased in the 5-HT response when a-AR antagonist was preincubated ($p<0.05$). **Conclusions:** a- and b-adrenergic receptors enhance the serotonin-induced contraction in guinea pig aorta. This contractile activity is modulated by mechanism involving the movement of $Ca^{2+}i$ and maybe through 5-HT receptors presynaptic activation.

**Disclosures: D.M. Mejía:** None. **P. Segura Medina:** None. **V. Carbajal Salinas:** None. **M. Vargas Becerra:** None. **E. Torrejón González:** None. **P. Campos Bedolla:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.19/NN4

**Topic:** F.07. Autonomic Regulation

**Support:** NIH R01 HL122829

**Title:** Co-inhibition of neurons in the rostral ventrolateral medulla by GABA and Glycine

**Authors: H. GAO**, *A. DERBENEV
Dept of Physiol., Tulane Univ., New Orleans, LA

**Abstract:** Presympathetic neurons in the rostral ventrolateral medulla (RVLM) are best known for their contribution to the control of sympathetic nervous system and homeostatic functions of the body. Both glycine and GABA were identified as fast inhibitory neurotransmitters in the RVLM. However, the mechanisms of GABA and glycine release and/or co-release in the RVLM remain to be determined. Whole-cell, patch-clamp recordings were conducted from presympathetic neurons identified with PRV-152, to investigate GABAergic and glycinergic inhibitory mechanisms in rat brainstem slices containing RVLM neurons. We tested the hypothesis that the release of glycine is associated with the activity of neuronal network. Our data revealed that inhibitory postsynaptic currents (IPSCs) recorded from RVLM neurons composed from both GABAergic and glycinergic synaptic events. In steady state conditions, GABA is the predominant inhibitory neurotransmitter in the RVLM. Surprisingly, after activation of the inhibitory network, the GABAergic and glycinergic neurotransmission were reversed. Under resting condition, the proportion of glycinergic IPSCs was less than 10% of the total IPSCs. Activation of the inhibitory network produced saturation of inhibitory events mediated by GABA and increased the average frequency of glycine-mediated IPSCs. After network activation, glycinergic IPSCs represent more than half of the total IPSCs in the RVLM. Our data suggest that glycinergic inhibition provides a secondary synaptic inhibition in presympathetic RVLM neurons. This novel mechanism has the potential for fine tuning of the sympathetic output controlling homeostatic functions.

**Disclosures: H. Gao:** None. **A. Derbenev:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.20/NN5

**Topic:** F.07. Autonomic Regulation

**Support:** CONACYT 252702

**Title:** Analysis of the vasodepressor responses induced by NaHS, sodium nitroprusside and acetylcholine in rats treated with high fat diet

**Authors: *C. B. GOMEZ**[1], M. BECERRIL-CHACÓN[2], E. GUTIÉRREZ-LARA[1], A. SÁNCHEZ-LÓPEZ[1], D. CENTURION[1]
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**Abstract:** Endothelial and vascular dysfunction is reported in isolated arteries from rats treated with high fat diet. However, up to date, it is unknown whether this effect is observed in the complete systemic vasculature in vivo. Thus, the aim of this study was to determine the effect of high fat diet on the vasodepressor responses to NaHS, acetylcholine or sodium nitroprusside in pithed rats infused with methoxamine. This experimental model allows evaluating the cardiovascular responses without the influence of the central nervous system. For this purpose, 12 animals were divided into two groups. The first group (n=6) was treated with normal diet and the second group (n=12) was treated with high-fat diet with lard 30% during 12 weeks. Next, body weight, blood triglyceride levels as well as blood glucose and plasma insulin were determined before postprandial glucose. In both groups the blood glucose and plasma insulin were determined after administration of glucose (1 g Kg-1, p.o.) at 5-120 min. Then, rats were: (1) anaesthetized with isoflurane; (2) pithed with a stainless steel road; (3) assisted with artificial ventilation; (4) cannulated for i.v. administration of several drugs; and (5) infused with methoxamine (20 μg Kg-1 min-1). The vasodepressor effects to i.v. administration of NaHS (1-10 mg Kg-1), acetylcholine (0.03-10 μg Kg-1) and sodium nitroprusside (0.56-18 μg Kg-1) were determined in animals infused with methoxamine. High fat diet produced increases in body weight without significant changes in basal blood glucose, basal plasma insulin or HOMA index or blood triglycerides. However, high fat diet significantly decreased glucose tolerance after administration of 1 g Kg-1 glucose (p.o.) while plasma insulin levels remained unchanged. Furthermore, i.v. administration of NaHS, acetylcholine and sodium nitroprusside elicited dose dependent vasodepressor responses in either animals treated with normal diet or high fat diet. These responses were not significantly different in both groups. The above results suggest that high fat diet induced obesity but not insulin resistance and produced no significant changes in the vasodepressor responses to the above drugs in systemic vasculature.

**Disclosures: C.B. Gomez:** None. **M. Becerril-Chacón:** None. **E. Gutiérrez-Lara:** None. **A. Sánchez-López:** None. **D. Centurion:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.21/NN6

**Topic:** F.07. Autonomic Regulation

**Title:** A cholinergic network for coordinating locomotor and sympathetic activities

**Authors: *J.-R. CAZALETS**[1], M. SOURIOUX[2], S. S. BERTRAND[3]
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**Abstract:** The onset of locomotion, as any other forms of physical activity, mobilizes the autonomic nervous system to match the increasing physiological demand. These autonomic responses mostly rely on the coupling between sympathetic and somatic motor activity. We know that cholinergic neuromodulation plays an important role in the control of locomotor networks; moreover several lines of evidences also suggest that spinal cholinergic input may activate sympathetic intermediolateral (IML) neurons. Here, using an isolated *in vitro* spinal cord from neonatal rat in which the autonomic and the locomotor networks remain intact, we show that application of a muscarinic receptor agonist (oxotremorine) induces synchronized oscillations of sympathetic intermediolateral neurons and somatic motoneurons. When the cord was partitioned at T13 level and oxotremorine was applied to the thoracic compartment, both thoracic and lumbar segments displayed synchronized oscillations, suggesting a leading role of thoracic neurons over lumbar network. Finally, this coordination between rhythmogenic networks responsible for two different motor functions provide the first evidence for the existence of a cholinergic activated spinal network that specifically synchronizes somatic to sympathetic outflow in the newborn rat spinal cord.

**Disclosures: J. Cazalets:** None. **M. Sourioux:** None. **S.S. Bertrand:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.22/NN7

**Topic:** F.07. Autonomic Regulation

**Support:** Conacyt Mexico Grant 252702

**Title:** Effect of chronic administration of estradiol on the vasopressor responses induced by the sympathetic nervous system in rats with fructose induced insulin resistance

**Authors: *E. J. GUTIÉRREZ**[1], A. SÁNCHEZ-LÓPEZ[1], M. E. BECERRIL-CHACÓN[1], M. B. RAMÍREZ-ROSAS[2], D. CENTURIÓN[1]
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**Abstract:** During aging, women and men experience an increase in cardiovascular risk. In the reproductive period, women have a lower prevalence of hypertension than men, whereas after menopause this relationship is reversed. After age 50, women have a higher prevalence of

hypertension compared to aged-matched men. These evidences suggest that estradiol may be involved in the development of hypertension. Some evidence suggests that diabetes suppresses female advantage and eliminates differences in risk of developing cardiovascular disease in premenopausal women. The objective of this study was to analyse the effect of 17β-estradiol on the cardiovascular responses induced by sympathetic stimulation or by several agonists in rats with fructose-induced insulin resistance. Thus, the vasopressor responses induced by sympathetic stimulation or i.v. bolus injections of the agonists noradrenaline (endogenous ligand), methoxamine ($\alpha_1$) and UK 14,304 ($\alpha_2$) were determined in female rats with fructose-induced insulin resistance or control rats pretreated with: (1) estradiol or (2) its vehicle (oil). For this purpose, animals were treated with fructose or its vehicle (water; control) during 16 weeks. After this time, both groups were divided into two subgroups: (1) sham-operated and (2) ovariectomized (ovx) rats. Next, both subgroups were subcutaneously treated with either: (1) estradiol (10 mg/kg) or (2) its vehicle (oil; 1 ml/kg) daily during 35 days. Then, under anaesthesia with isoflurane, animals were pithed and prepared to measure blood pressure and heart rate. In sham operated rats, insulin resistance diminished the vasopressor responses to sympathetic stimulation, noradrenaline and UK 14,304 while responses to methoxamine remained unchanged. In ovariectomized rats, insulin resistance did not change the vasopressor responses. On the other hand, in control animals, ovariectomy significantly decreased the vasopressor responses to sympathetic stimulation and noradrenaline while in fructose-fed rats ovariectomy did not change the above cardiovascular responses. Interestingly, in ovariectomized rats, 17β-estradiol: (1) increased sympathetic stimulation responses in animals treated with fructose; (2) diminished noradrenaline responses in control animals; (3) did not modify the responses to methoxamine and UK 14,304 in control or fructose-induced insulin resistance. These data suggest that 17β-estradiol is capable to restore the decreases in the vasopressor responses to sympathetic stimulation observed during insulin resistance.

**Disclosures:** **E.J. Gutiérrez:** None. **A. Sánchez-López:** None. **M.E. Becerril-Chacón:** None. **M.B. Ramírez-Rosas:** None. **D. Centurión:** None.

**Poster**

**506. Cardiovascular Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 506.23/NN8

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant HL 133862

American Autonomic Society postdoctoral fellowship to J.Dyavanapalli

**Title:** Activation of hypothalamic oxytocin neurons restores oxytocin release to parasympathetic cardiac vagal neurons of the brainstem in left ventricular hypertrophy induced heart failure

**Authors: *J. DYAVANAPALLI**[1], D. MENDELOWITZ[2]
[1]George Washington Univ. Dept. of Pharmac, Washington, DC; [2]George Washington Univ., Washington, DC

**Abstract:** Heart failure (HF), is characterised by an autonomic imbalance i.e., high sympathetic and depressed parasympathetic activities to the heart. Oxytocin, traditionally involved in promoting lactation and uterine contractions, has been known to improve stress induced changes in autonomic balance. Parasympathetic activity to the heart originates from cardiac vagal neurons (CVNs) in the brainstem, whose activity has been shown to be controlled, in part, by excitatory synaptic input co-releasing oxytocin from hypothalamic paraventricular nucleus oxytocin neurons (PVN). Activation of PVN oxytocin neurons is crucial for the activation of CVNs that increases parasympathetic activity to the heart. This study tests if activation of oxytocin neurons restores oxytocin release to activate CVNs and hence increases parasympathetic activity to the heart that is diminished in left ventricular hypertrophy induced heart failure (HF). Left ventricular hypertrophy was elicited in rats by aortic pressure overload using a transaortic constriction (TAC) approach. Selective activation of PVN OXT fibers projecting to CVNs was achieved by chemogenetic DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) and optogenetic Channelrhodopsin (ChR2) approach. A cocktail of viral vectors, cre expression under OXT promoter (AAV1-OXT-Cre) +floxed DREADDS (AAV2-DIO-HM3Dq-mcherry) + floxed ChR2 (AAV1-EF1a-DIO-hChR2) were co-injected in to the PVN. 3 groups of animals Sham , TAC and TAC+Treatment (activation of DREADDS by daily injection of CNO) were used to assess oxytocin release upon photoactivation of PVN ChR2 fibers surrounding CVNs at 2,4 and 6 weeks post-surgery using cultured Chinese hamster ovary cells co-expressing OXT receptors and $Ca^{2+}$ indicator, R-GECO. There were no changes in calcium responses in CHO cells trigged by photoactivation of PVN ChR2 fibers neibouring CVNs among 2, 4 and 6 weeks post sham. However, there is a blunted activation of CHO cells at 6 weeks post TAC compared to 2 and 4 wks post Tac groups (% increase in fluorescence: 18.6 ± 2.6 at 2 wks, n=9; 19.2 ± 2.0 at 4 wks, n=16 and 10.5 ± 1.5, n=16 at 6 wks post Tac). Further, the blunted CHO cell responses at 6 wks post Tac were completely restored by activation of PVN OXT neurons at 6 wks post TAC+Treatment (21.6 ± 2.0; n=22 in sham, 10.5 ± 1.5; n=16 in TAC and 25.1 ± 1.6; n=22 in TAC+Treatment). These results indicate reduced PVN release of oxytocin onto CVNs likely contributes to depressed parasympathetic cardiac activity in HF. Hypothalamic oxytocin neuron activation may restore CVN activity and blunt cardiovascular dysfunction in HF.

**Disclosures: J. Dyavanapalli:** None. **D. Mendelowitz:** None.

**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.01/NN9

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant NIH/NIGMS R01 GM083108

NIH Grant NHLBI R01HL111621

NIH Grant NHLBI U01 HL133360

NIH Grant T32AA007463-28

**Title:** Novel brain microrna therapy treats hypertension

**Authors: J. GORKY**, D. DECICCO, R. VADIGEPALLI, *J. S. SCHWABER
Pathol, Daniel Baugh Inst., Philadelphia, PA

**Abstract:** Decades of research on spontaneously hypertensive rat (SHR) model of hypertension have suggested that essential hypertension occurs as a result of perturbations in the blood pressure control network. Previous work has found perturbations in the kidney, the carotid body, and the nucleus of the solitary tract (NTS) each to be sufficient to control hypertension. Within each organ system too, there are claims that one signaling pathway or another is the primary driver of hypertension. Instead, it may be more useful to consider hypertension as the emergent property of a network that has been pushed out of a normotensive equilibrium into a compensatory, yet ultimately pathological state. The crosstalk between and within organ systems can be largely represented by an interconnected set of gene regulatory networks. In this work, we show that small perturbations in the gene regulatory networks in the NTS by selectively blocking two microRNAs (miR-135a and miR-376a) are sufficient to lower blood pressure in the SHR model. Furthermore, this effect appears driven by only modest changes in putative gene targets of these miRNAs, suggesting that the *combination* of genes that are targeted in the network is responsible for the effect rather than just one gene or another. While the use of anti-sense oligonucleotides to treat hypertension is itself novel, the demonstration that hypertension is the consequence of network emergence suggests new treatment paradigm altogether is needed.

**Disclosures: J. Gorky:** None. **D. DeCicco:** None. **R. Vadigepalli:** None. **J.S. Schwaber:** None.

**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.02/NN10

**Topic:** F.07. Autonomic Regulation

**Support:** NIH R01 NR-013625

NIH R01 NR-014669

**Title:** Association of depressive symptoms with regional brain tissue integrity in heart failure

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**Abstract:** Heart failure (HF) patients often feel depressed, which prevent them performing routine activity leading to recurrent hospitalization and increased mortality. Multiple brain regions in HF show tissue damage, but associations between regional brain tissue integrity and depressive symptoms are unclear. T2-relaxometry procedure is known to show brain injuries in patients with HF, and this method may be useful here to examine such relations. Our aim was to assess relationships between brain tissue integrity and depressive symptoms in HF subjects using T2-relaxometry procedures. Proton-density and T2-weighted images were acquired from 12 HF (age, 54.3±8.6 years; 9 male; BMI, 29.3±6.4 kg/$m^2$; LVEF, 26.3±6.4%; NYHA functional class II/III 94/6%), using a 3.0-Tesla MRI scanner, and depressive symptoms were examined with the Zung Self-Rating depression scale (ZSDS) questionnaire. Whole-brain T2-relaxation maps were computed, normalized, and smoothed. The smoothed T2-relaxation maps were used to examine associations between regional brain tissue status (higher T2-relaxation indicates more injury) and individual ZSDS scores (higher scores show severe depression) in HF subjects voxel-by-voxel using partial correlation procedures (SPM12; covariates, age, gender; uncorrected threshold $p<0.005$). Significant positive correlations ($p<0.005$) between regional T2-relaxation values and ZSDS scores appeared in several sites, including inferior and mid temporal gyrus, right cerebellar cortex, cerebellar vermis, basal forebrain, external and internal capsule, pons extending to mid-brain, pre-frontal and frontal cortices, occipital and parietal cortices, amygdala. Negative correlations between T2 values and ZSDS scores emerged only in cerebellum. HF subjects show significant correlations between depressive symptoms and brain tissue integrity in areas that control mood function. The findings suggest that site-specific brain injuries are promoting to depressive symptoms, consequently contributing to increased morbidity and mortality. Therapeutic strategies should be developed to reduce brain injury, which may greatly impact mood function and improve the prevailing condition.

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**Poster**

**507. Cardiovascular Regulation II**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.03/NN11

**Topic:** F.07. Autonomic Regulation

**Support:** CAPES

Fapemig

UFOP

CNPq

NIH 1R01HL119380

**Title:** The brain renin angiotensin system (RAS) is upregulated in sympathetic control regions in a female rodent model of anorexia nervosa

**Authors: *A. ARLINDO DE SOUZA**[1,2], G. S. CAMPOS[1], L. G. B. SANTOS[1], A. PAI[3], A. LINARES[5], R. C. SPETH[6,4], H. JI[2], D. A. CHIANCA, Jr[1], R. C. A. MENEZES[1], K. SANDBERG[2]
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**Abstract:** Anorexia nervosa is associated with cardiovascular dysfunction including ventricular hypertrophy, hypotension and bradycardia due to severe food restriction (**FR**). Two weeks of FR in female Fischer rats models the cardiovascular dysfunction observed in anorexia including increased activity of the peripheral angiotensin type 1 receptor (**$AT_1R$**). The goal of this study was to evaluate the effect of FR on the expression and function of the $AT_1R$ and levels of angiotensin (**Ang**) peptides in brain regions that regulate the sympathetic nervous system (**SNS**) since the brain RAS regulates SNS. Food intake was reduced by 60% for two weeks in Fischer female rats (200g body weight). At day 7, a guide cannula was placed in the lateral ventricle and on day 14, the femoral artery was catheterized to record mean arterial pressure (MAP) and heart rate (HR). A parallel group of animals were used for measuring Ang peptides by LC-MS/MS and $AT_1R$ expression by receptor autoradiography in brain regions involved in SNS control. FR reduced body weight by ~12%, $p<0.05$; MAP by ~8 mm Hg, $p<0.05$; and HR by ~29 bpm, $p<0.05$; compared to control (CT) rats. Intracerebroventricular (icv) injection of Ang-[1-10] caused a higher pressor response ($p<0.005$) in FR compared to CT even though icv Ang-[1-8] reduced MAP in FR rats ($p<0.02$) without altering HR. Similar responses were observed after icv injection of Ang-[1-7] ($p<0.0001$). Losartan administered icv lowered MAP more in FR compared to CT rats ($p<0.03$). FR increased $AT_1R$ binding in the paraventricular nucleus ($p<0.005$) and in the rostral ventrolateral medulla ($p<0.05$). No differences in $AT_1R$ binding were observed in the amygdala, subfornical organ, vascular organ of lamina terminalis, median preoptic nucleus, solitary tract nucleus and caudal ventrolateral medulla. After spiking samples with Ang-[1-8], both Ang-[1-8] ($p<0.05$) and Ang-[3-7] ($p<0.05$) were increased in the brainstem of FR compared to CT rats. We also observed an increase in Ang-[1-8] ($p<0.0005$), Ang-[2-8] ($p<0.05$) and Ang-[3-8] ($p<0.05$) in the hypothalamus in the FR compared to the CT group. When the samples were spiked with Ang-[1-10], there was a decrease in Ang-[1-10] ($p<0.005$) and an increase in Ang-[1-7] ($p<0.05$) in the brainstem, and only Ang-[2-10] ($p<0.05$) was increased in the hypothalamus. These results suggest that increased AT1R activity mediated

by Ang-[1-7] and Ang-[1-8] in the paraventricular nucleus and rostral ventrolateral medulla contribute to the increased SNS activity observed in FR rats and in women with anorexia nervosa.

**Disclosures: A. Arlindo De Souza:** None. **G.S. Campos:** None. **L.G.B. Santos:** None. **A. Pai:** None. **A. Linares:** None. **R.C. Speth:** None. **H. Ji:** None. **D.A. Chianca:** None. **R.C.A. Menezes:** None. **K. Sandberg:** None.

**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.04/NN12

**Topic:** F.07. Autonomic Regulation

**Support:** HSFO

**Title:** Carotid chemo-and baro-receptor in the ovariectomized and estrogen treated female

**Authors: *J. CIRIELLO**[1], M. MAXIMOS[2], C. V. R. DE OLIVEIRA[3]
[2]Physiol. and Pharmacol., [3]Anat. and Cell Biol., [1]Univ. Western Ontario, London, ON, Canada

**Abstract:** The effects of 17β-estradiol (E) in ovariectomized (OVX) females on the distribution of carotid chemo- and baro-receptor afferent fibers was investigated using the transganglionic transport of a mixture of wheat germ agglutinin- (2%) and cholera toxin B-subunit- (5%) conjugated horseradish peroxidase (HRP). Tract-tracing experiments were done in age matched adult OVX only or OVX + E (30 pg/ml plasma) Wistar rats. The combined HRP solution was applied directly to the carotid sinus nerve (CSN), carotid body (CB) and carotid sinus (CS). After application of HRP to the CSN or CB in both groups of females, the distribution of fiber and presumptive terminal labeling in the ipsilateral nucleus of the solitary tract (NTS) complex was found to be greater in the OVX only female compared to OVX + E treated female for both the CSN and CB. However, the density of the projections was greater after CSN labeling. In both groups of females, dense fiber and presumptive terminal labeling was found within the dorsolateral (Sdl), medial (Sm) and commissural subnuclei, and nucleus gelatinous of the NTS complex. Additionally in the OVX only females, at and just caudal to area postrema (ap), labeled fibers were found to course through and around the ventrolateral NTS subnucleus and between the dorsal motor nucleus of the vagus and hypoglossal nucleus before turning and heading towards the ventrolateral reticular formation. Most of these labeled fibers appeared to terminate within the nucleus ambiguus (Amb) and in a region immediately caudal and ventral to Amb. After application of HRP to the CS in either group of females, afferent labeling was found restricted to the ipsilateral NTS complex only, primarily within the Sdl, Sm and interstitial subnucleus. The CS projections in the OVX + E treated females were overall denser than those

found in OVX only females. Furthermore, CS projections to NTS overall were considerable less than those observed that originated in the CB. Taken together, these data suggest that cardio-respiratory differences observed between pre-and post-menopausal females may be related in-part to medullary afferent connections of chemo- and baro-receptors. Supported in part by a grant from HSFO of Ontario.

**Disclosures: J. Ciriello:** None. **M. Maximos:** None. **C.V.R. de Oliveira:** None.

**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.05/NN13

**Topic:** F.07. Autonomic Regulation

**Title:** Behavioral and pharmacological interactions on heart rate and performance on the rotarod endurance and coordination test

**Authors: *A. L. ZMAROWSKI**[1], S. REED[1], B. VISNICK[1], M. A. HAWK[2], R. LORDO[1], T. VINCI[1]
[2]Safety Pharmacol., [1]Battelle, West Jefferson, OH

**Abstract:** The safety pharmacology core battery investigates potential adverse effects of pharmaceuticals on the function of vital organ systems including the cardiovascular and central nervous systems (CNS). However, these systems are rarely examined in parallel. Drugs may have different effects under resting or stimulated conditions, and therefore the simultaneous investigation of cardiovascular and neurobehavioral endpoints provides a more thorough evaluation of drug safety assessment. This study was conducted to evaluate cardiovascular changes during baseline performance in neurobehavioral tests and after treatment with pharmacological agents. Animals were implanted with telemetry units monitoring blood pressure (BP) and heart rate (HR). After surgical recovery, animals were tested for endurance and coordination in the Rotarod test. Animals were tested for 4 trials per day for up to 6 minutes per trial after treatment with vehicle (water for injection), amphetamine (AMPH, 1 and 2 mg/kg), MK-801 (0.1 and 0.15 mg/kg) and Diazepam (DIAZ, 5 and 10 mg/kg). The initial rotational speed was 4 revolutions per minute (RPM) that accelerated to 40 RPM over the test duration. HR and BP increased with placement on the rotarod and was further elevated with acceleration over time. After falling, HR rapidly decreased and remained low during the inter-trial interval (ITI) time. AMPH improved performance with animals maintaining rotarod performance longer than with vehicle. AMPH elevated HR in general, and during rotarod performance, though HR was not increased further with accelerating Rotarod speed and BP was not impacted. HR and BP were highest of all treatments with MK-801 and stayed elevated during the ITIs. However, animals could not maintain performance, falling off almost instantly. DIAZ reduced HR, BP, and

performance during rotarod testing. The combined assessment of physiological and behavioral endpoints provides a more complete evaluation of drug-induced effects under baseline and stimulated conditions and thereby improve overall pharmaceutical safety testing.

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**Poster**

**507. Cardiovascular Regulation II**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.06/NN14

**Topic:** F.07. Autonomic Regulation

**Support:** Health Professions Division, Nova Southeastern University

Cardiovascular Neuroscience Research Fund, Nova Southeastern University

**Title:** Brain $AT_1$ angiotensin receptor binding and hippocampal gene methylation in Dahl salt-sensitive hypertensive rats as a function of ovariectomy

**Authors: *R. C. SPETH**[1,3], H. W. PANG, 33328[1], A. LINARES[1], N. ROSE, 33328[1], D. PATEL[2], A. V. PAI[4], A. A. DE SOUZA[4], E. J. POLLNER[4], C. A. WEST[4], M. S. TRIVEDI[1], H. JI[4], K. SANDBERG[4]
[1]Dept. of Pharmaceut. Sciences, Col. of Pharm., [2]Dept. Biology, Halmos Col. of Natural Sci. and Oceanography, Nova Southeastern Univ., Davie, FL; [3]Pharmacol. and Physiol., [4]Med., Georgetown Univ., Washington, DC

**Abstract:** Women are resistant to hypertension and cardiovascular disease prior to menopause due to the protection afforded by ovarian hormones. After menopause, women are not only more susceptible to cardiovascular disease, they are also more susceptible to mild cognitive impairment and conversion to dementias. Accumulating studies indicate the brain angiotensin system (**BAS**) plays a role in cognitive function in addition to its ability to regulate the cardiovascular system. Therefore, the aim of this study was to assess the effect of ovarian hormone loss on the BAS and gene expression in the hippocampus of the hypertensive Dahl salt-sensitive (**DS**) rat, an animal model of salt-sensitive human hypertension. $AT_1R$ binding was determined autoradiographically in selected brain regions of female hypertensive DS and normotensive Dahl salt-resistant (**DR**) rats that were ovariectomized (**OVX**) or sham-operated (**SHAM**) at 13 weeks of age and sacrificed at 33 weeks of age. In addition, DNA methylation was assessed by ELISA in the hippocampus. Mean arterial blood pressure (MAP) and heart rate (HR) were determined telemetrically (DSI technology) at 29 weeks of age. The MAP of DS sham rats was 181±5 mm Hg while the MAP of DR sham rats was 96±4 mm Hg ($p<0.0001$).

Ovariectomy did not significantly increase MAP in either strain. The HR of the DS sham rats was 426±8 bpm, while the MAP of he DR sham rats was 344±3 bpm ($p<0.0001$). Ovariectomy did not significantly alter HR in either strain. $AT_1R$ expression in the solitary tract nucleus of the DS-OVX rats was significantly reduced ($p<0.05$) from that of the DR-OVX and the intact DS-SHAM rats. There were no differences in $AT_1R$ expression in the piriform cortex, organum vasculosum of the lamina terminals, median preoptic nucleus, subfornical organ, paraventricular hypothalamic nucleus, suprachiasmatic nucleus, and lateral hypothalamus as a function of strain or ovarian hormone status. Global DNA methylation was also reduced in the hippocampus of DS-OVX rats relative to DS-SHAM ($p<0.01$) and DR-OVX ($p<0.05$). These results suggest that strain differences and gonadal functionality have a limited effect on brain $AT_1R$ expression and that the change that does occur is a reduction in $AT_1R$ expression in the nucleus tractus solitarius of the OVX hypertensive strain of female rats. The global DNA methylation changes suggest alterations in gene expression in the hippocampus of the DS-OVX rat. Further studies will be directed to determining which genes are affected at the epigenetic and gene expression level in the hippocampus.

**Disclosures:** **R.C. Speth:** None. **H.W. Pang:** None. **A. Linares:** None. **N. Rose:** None. **D. Patel:** None. **A.V. Pai:** None. **A.A. De Souza:** None. **E.J. Pollner:** None. **C.A. West:** None. **M.S. Trivedi:** None. **H. Ji:** None. **K. Sandberg:** None.

**Poster**

**507. Cardiovascular Regulation II**

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**Topic:** F.07. Autonomic Regulation

**Support:** FAPESP

CNPQ

**Title:** Decrease in synaptic transmission induced by anoxia in NTS is prevented by short-term sustained hypoxia

**Authors: *D. ACCORSI-MENDONCA**[1], L. G. H. BONAGAMBA[1], B. H. MACHADO[2]
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**Abstract:** Neurons are highly sensitive to tissue oxygen level and decrease in oxygen (hypoxia or anoxia) produces modifications in neurotransmission as well in the intrinsic excitability of these cells. Moreover, during the hypoxia the peripheral chemoreflex is activated and produces cardiovascular and respiratory changes to keep the oxygen level in the physiological range. In this study we evaluated the effect of short-term sustained hypoxia [SH (24 hours, $FiO_2$ 10%)] on

the alterations induced by anoxia (5 min) on neurotransmission at the NTS, the first synaptic station of peripheral chemoreflex afferents in the brainstem. For this purpose, we used whole-cell patch clamp technique and brainstem slices of Wistar rats (30 days old). During the experiments normoxia condition were obtained by bubbling the bath solution with 95% $O_2$ e 5% $CO_2$ and for the anoxia condition the bath solution was bubbled with 95% $N_2$ e 5% $CO_2$. We observed that anoxia induced a hyperpolarization (-5 ± 0.2 mV in membrane voltage) and blocked the spontaneous fire frequency in NTS neurons from control rats. However, the SH exposure prevented the anoxic effects on the membrane voltage and in the fire frequency; after anoxia NTS neurons from SH rats preserved spontaneous firing (45 ± 8.5 % of firing rate in normoxia). Anoxia reduced the amplitude of evoked glutamatergic current in the NTS neurons from control group [142 ± 25 pA vs 91 ± 27 pA, $p<0.0001$ (n=14)] as well in SH group [319 ± 73 pA vs 232 ± 68 pA, $p<0.001$ (n=12)] and did not change the resting membrane potential in both groups [control group: -63 ± 3 mV vs -64 ± 7 mV (n=5); SH group: -62 ± 4 mV vs -66 ± 3.2 pA, (n=4)]. These data are showing that the short-term SH prevented the reduction in fire frequency and changes in membrane voltage induced by anoxia in NTS neurons.

**Disclosures: D. Accorsi-Mendonca:** None. **L.G.H. Bonagamba:** A. Employment/Salary (full or part-time):; University of São Paulo. **B.H. Machado:** A. Employment/Salary (full or part-time):; University of Sao Paulo.

**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.08/NN16

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant HL36520

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NIH 1ZIAES070065

**Title:** Estrogen receptor beta regulates basal blood pressure and NMDA receptor-mediated signaling in the female mouse hypothalamic paraventricular nucleus and contributes to hypertension associated with accelerated ovarian failure

**Authors: *T. A. MILNER**[1], G. WANG[1], T. A. VAN KEMPEN[1], E. M. WATERS[2], B. S. MCEWEN[2], K. S. KORACH[3], M. J. GLASS[1]
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**Abstract:** The increased sensitivity to hypertension as women enter menopause may involve alterations in estrogen signaling in neural systems regulating the control of sympathetic output, yet the mechanisms mediating these actions are unclear. We report that estrogen receptor ß (ERß) activation in the hypothalamic paraventricular nucleus (PVN), a critical coordinator of sympathetic function, contributes to basal blood pressure and modulates excitatory neuronal signaling. At the functional level, spatial-temporal deletion of ERß in the PVN of female mice (2 months of age) resulted in an increase in blood pressure in the absence of ovariectomy or a hypertensive stimulus. At the cellular level, ERß was strategically localized to dendrites of PVN neurons receiving excitatory inputs that have been shown to be critical in regulating sympathoexcitatory output. Many of these dendrites also contained the NMDA-type glutamate receptor, whose activation is an important modulator of blood pressure. Importantly, in PVN slices of female mice, application of the ERß agonist diarylpropionitrile (DPN) significantly decreased the NMDA-mediated depolarization of PVN neurons. The NMDA-mediated increase in firing rate was also returned to baseline values by DPN. The role of ERß also was evaluated in the 4-vinylcyclohexene diepoxide (VCD) mouse model of accelerated ovarian failure (AOF). In VCD treated mice, 14-day administration of a slow-pressor dose of angiotensin II (AngII) resulted in an increase in blood pressure at a stage of ovarian failure comparable to perimenopause in women. Significantly, the hypertensive response to AngII was blocked in mice given cyclic systemic administration of DPN (1mg/kg, I.P. for 2 days followed by two days off repeated over the 2 week period). These results indicate that ERß in the PVN of female mice is an important regulator of basal blood pressure and a modulator of NMDA receptor-mediated excitatory signaling. In addition, ERß may also be a significant player in the emergence of AngII-dependent hypertension in peri-AOF mice. These results suggest a novel neural mechanism for the actions of estrogen in blood pressure control. They also provide further support that perimenopause is a therapeutic window of opportunity for estrogen-based management of hypertension as women transition through menopause.

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**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.09/NN17

**Topic:** F.07. Autonomic Regulation

**Support:** FAPESP

UNINOVE CAPES PROSUP

**Title:** Characterization of social behaviours, neurogenic pain and hemodynamic parameters in the model of acute intermittent porphyria

**Authors: *C. A. PENATTI**[1], R. F. BARROS[1], I. C. SANCHES[2], S. C. FREITAS[1], K. DE ANGELIS[1]
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**Abstract:** Acute intermittent porphyria (AIP) is one of the main forms of congenital porphyria, an enzyme deficiency disorder in the biochemical pathway of heme formation, which affects individuals causing both peripheral (i.e. autonomic nerve dysfunction) and central (i.e. neuropsychiatric symptoms) nervous system (NS) disabilities such as neuropathic pain and hemodynamic imbalance as well as hallucinations and social behavior problems, respectively. Accumulation of 5-aminolevulinic acid (ALA), an early residue in the biosynthesis of heme, may act as the causal agent for these pathological effects in AIP. Using two rodent models of AIP, our goal was to search for and characterize changes in social behaviors in parallel to determine the disarrangements in hemodynamic response and pain threshold. For the behavioral and pain studies, we used the mouse strain C57BL/6 with both males and females. Male and female Wistar rats were used on experimental trials for accessing the hemodynamic parameters. Upon long-term treatment using intraperitoneally high concentrations of ALA (40 mg/ml) on alternate days, we tested for behavioral paradigms of motor locomotion, exploratory behavior and anxiety level, neuropathic pain and offensive aggressiveness in C57BL/6 mice. The hemodynamic parameters were assessed both non-invasively with ultrasound/color Doppler and invasively with direct recordings of blood pressure, heart rate and cardiovascular autonomic modulation by spectral analysis in Wistar rats. Behavioral paradigms showed that long-term treatment with ALA promoted an important reduction in motor locomotion in both male and female mice and very low propensity for offensive aggression in males relative to controls. In addition, there was a marked increase in the perception of pain. Our method with ultrasound/Doppler accessed the blood flow of mesenteric-portal venous system, which presented lower blood flow in ALA-treated rats. ALA-induced reduction in mean blood pressure was observed in males with no differences in heart rate (HR). In the HR variability analysis, there was a decrease in both pulse interval (PI) variance and PI standard deviation in the ALA group. ALA-induced autonomic changes could be observed with a decrease in high frequency and low frequency bands of PI, but without difference in symopathovagal balance. Systolic arterial pressure variability was also decreased in ALA group. Altogether, our study shows long-term NS changes in porphyria-like conditions, which may aid in the development of specific diagnostic tools and methods to access heme disorders-related clinical signs and to improve medical and rehabilitation care in affected individuals.

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**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

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**Program#/Poster#:** 507.10/NN18

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant R01-NR013930

NIH Grant R01-NR016463

**Title:** Brain axonal and myelin changes in patients with single ventricle congenital heart disease

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**Abstract:** Single ventricle congenital heart disease (SVCHD) patients show white matter injury in neighboring sites that control autonomic, mood, and cognitive functions, issues that are common in the condition. However, it is unclear whether SVCHD subjects have predominantly axonal or myelin injury. Diffusion tensor imaging (DTI)-based axial diffusivity (AD), which measures water diffusion parallel to fibers and shows axonal changes, and radial diffusivity (RD), which measures water diffusion perpendicular to fibers and indicates myelin changes, may be useful to examine such differences in SVCHD subjects. In this study, our aim was to examine regional brain axonal and myelin changes in SVCHD patients compared to healthy controls using DTI-based AD and RD procedures. We collected two separate DTI series from 12 SVCHD (age, 15.7±1.1 years; body mass index, 20.9±3.0 kg/m$^2$; 6 male) and 27 control subjects (age, 15.8±1.1 years; body mass index, 22.3±5.3 kg/m$^2$; 14 male) using a 3.0-Tesla magnetic resonance imaging scanner. Whole-brain AD and RD maps were calculated from each series, realigned and averaged, normalized to a common space, and smoothed. The smoothed AD and RD maps were compared between groups using analysis of covariance, with age and gender included as covariates (uncorrected threshold, $p<0.001$; extended cluster size, 10 voxels). No significant differences in age, body-mass-index, or gender appeared between SVCHD and control subjects. SVCHD subjects showed increased AD and RD values in multiple brain sites, although AD changes were more wide-spread, including the prefrontal and frontal gyrus, precentral and post-central gyrus, anterior, mid, posterior cingulate, corpus callosum, insular sites, hippocampus and parahippocampal gyrus, amygdala, mammillary bodies, pons, cerebellar cortex, occipital and temporal gyri, thalamus, and parietal area, compared to controls. Adolescents with SVCHD show significantly increased AD and RD values, indicating loss of both axonal and myelin integrity in brain areas that regulate autonomic, mood, and cognitive

functions. These findings may result from delayed brain development in early stage of life or hypoxia/ischemia induced processes accompanying the condition.

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**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.11/NN19

**Topic:** F.07. Autonomic Regulation

**Title:** Brain inflammation in streptozotocin-treated diabetic rats contributes to development of cardiovascular complications and is modulated by oral saline intake

**Authors: O. AL ZAHRANI**[1], E. ALAHMADI[2], H. HABEEBALLAH[1], E. BADOER[1], *M. J. STEBBING[1]
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**Abstract:** We have previously shown that microglia become activated within cardiovascular control centres in the brains of streptozotocin (STZ) treated diabetic rats and not in surrounding areas. In the paraventricular nucleus (PVN), microglial activation is not seen until 6 weeks after induction of diabetes and is preceded by intense activation of PVN neurons associated with chronic dehydration and electrolyte imbalance (1). Others have shown that giving 1% saline to drink after induction of diabetes increases blood pressure in STZ-treated rats (2). We therefore investigated the relationship between PVN microglial activation, the development of diabetic cardiovascular complications and the effect of saline intake of both of these processes. Male Sprague Dawley rats were made diabetic with a single injection of STZ via the tail vein. Fluid intake and blood parameters were monitored throughout experiments in control rats and diabetic rats given tap water or saline to drink. Blood pressure was measured via tail cuff in conscious rats and cardiac function was studied under anaesthesia via echocardiography and ventricular pressure measurements. Microglial morphology was quantified using immunohistochemistry for cd11b (1). After 2 weeks, diabetic rats drinking 1% saline showed microglial activation in the PVN and elevated blood pressure, but control rats and diabetic rats drinking tap water did not. Inhibition of microglial activation via icv minocycline infusion prevented the increase in blood pressure in diabetic rats given saline. At 6 weeks post-STZ, diabetic rats given tap water showed elevated polydipsia, blood parameters consistent with dehydration, activation of PVN microglia, and functional signs of cardiomyopathy, but diabetic rats given 1% saline for 6 weeks did not, suggesting a delicate balance between electrolyte intake and electrolyte loss in these animals. In a separate set of experiments 0.9% saline intake did not increase blood pressure in STZ diabetic rats at 2 weeks and diabetic rats given low level insulin supplementation to prevent dehydration

showed no sign of cardiomyopathy even after 10 weeks of diabetes. We conclude that neuroinflammation in the PVN and other cardiovascular control centres, secondary to chronic fluid and electrolyte imbalances may contribute to the development of diabetic complications and preventing dehydration may be therapeutic. References: 1. Rana et al. J Neuroendocrinol. 2014 26:413-25. 2. Maeda et al. Clin Exp Pharmacol Physiol. 2007 34:574-80.

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**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.12/DP11/NN20 (Dynamic Poster)

**Topic:** F.07. Autonomic Regulation

**Title:** Post-stimulus persistent activation of the ventrolateral medulla in response to tetanic electrical stimulation of the hypothalamus analyzed by voltage imaging

**Authors: *Y. KONO**[1,2], H. ONIMARU[3], I. FUKUSHI[2], S. OKAZAKI[2,4], S. YOKOTA[5], K. TAKEDA[2,6], Y. HASEBE[1,2], K. KOIZUMI[1], K. SUGITA[1], Y. OKADA[2]
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**Abstract:** The central nervous system, especially the hypothalamus and the ventrolateral medulla, regulates the cardiovascular function. Pathological persistent activation of the central cardiovascular regulatory system has been thought to cause hypertension. Electrophysiological studies have shown that stimulation of the dorsomedial hypothalamus and paraventricular nucleus of the hypothalamus evokes augmentation of sympathetic nervous activity through excitation of the ventrolateral medulla. However, spatiotemporal dynamics of multicellular activities in the ventrolateral medulla in response to hypothalamic activation have not been well analyzed. In this study, we investigated how the ventrolateral medulla responds to electrical stimulation of the hypothalamus, by fluorescent optical imaging using a voltage-sensitive dye (voltage imaging) which allows us to visualize multicellular activities and to analyze their spatiotemporal dynamics. The brain stem spinal cord preparation containing the hypothalamus was isolated en bloc from the neonatal Wistar rat (P0-2) under deep anesthesia with isoflurane. The preparation was dyed with a voltage-sensitive dye (Di-2-ANEPEQ) that was solved in oxygenated artificial cerebrospinal fluid (aCSF). After dyeing, the preparation was fixed with the ventral side up in a recording chamber and continuously superfused with oxygenated aCSF at 26-

28°C. The viability of the preparation was confirmed by recording neural respiratory output from the 4th ventral root of the cervical spinal cord. Using a CMOS sensor array (MiCAM Ultima, BrainVision, Tokyo) connected with an epifluorescence microscope, we conducted voltage imaging of neural activity of the ventral medulla. We observed spread of depolarizing optical signals on the ventrolateral medulla evoked by electrical stimulation of the hypothalamus with 2 different modalities. One was single pulse stimulation which was 3 msec in pulse duration and 0.5 mA in intensity. The other was tetanic stimulation with 10 Hz and 0.4 mA in intensity for 10 sec. Single pulse stimulation evoked only brief excitation in the ventrolateral medulla, but tetanic stimulation induced excitation that persisted nearly 10 sec after the cessation of the stimulation. Observed prolonged excitation of the ventrolateral medulla induced by tetanic stimulation of the hypothalamus may partly explain the pathophysiological mechanism of hypertension. Also, this imaging method would contribute to unraveling the mechanism of cardiovascular regulation by the central nerve system.

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**Poster**

**507. Cardiovascular Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 507.13/NN21

**Topic:** F.07. Autonomic Regulation

**Support:** Fondecyt #1140275.

**Title:** RVLM C1 neuron ablation normalizes cardiorespiratory control in heart failure

**Authors: *R. DEL RIO**, D. C. ANDRADE, C. TOLEDO, H. S. DIAZ
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**Abstract:** Heart failure (CHF) is characterized by sympathoexcitation and breathing disorders. The rostral ventrolateral medulla (RVLM) is hyperactive in CHF. However, there is no direct evidence between the relationship of RVLM chronic hyperactivation, sympathoexcitation and progression of cardiac deterioration in CHF. We hypothesized that selective elimination of cathecolaminergic neurons from the RVLM delays cardiac deterioration in CHF rats. CHF was induced by volume overload in male Sprague-Dawley rats (250±20g). Ablation of C1 cells was performed by anti-dopamine-beta hydroxylase (DβH)–saporin toxin (DβH+SAP) injected into the RVLM. The degree of HF was estimated by echocardiography. Cardiac function was assessed by intraventricular PV loops. Arrhythmia index and breathing disorders were scored. Central and peripheral chemoreflex and cardiac autonomic control were also study. Partial

elimination of C1 RVLM neurons (≈50%) delay the decrease in fractional shortening in CHF rats (CHF+Veh: 59±5 vs. 45±1 %, $p<0.05$, pre vs. post vehicle, respectively; CHF+DβH-SAP: 57±4 vs. 51±4 %, $p>0.05$, pre vs. post toxin, respectively). In addition, compared to CHF vehicle treated rats, CHF+DβH-SAP rats showed (CHF+Veh vs. CHF+DβH-SAP, respectively): i) a reduced cardiac sympathetic drive (-98±12 vs. -52±7 ΔHR, $p<0.05$), ii) an improvement in both cardiac diastolic (0.009±0.001 vs. 0.004±0.001 mmHg/µl, $p<0.05$) and systolic function (0.2±0.01 vs. 0.5±0.1 mmHg/µl, $p<0.05$), iii) a reduced number of arrhythmias (95±20 vs. 48±14 events/hour, $p<0.05$), and iv) a reduced incidence of breathing disorders (9±1 vs. 6±1 apneas/hour, $p<0.05$). Finally, the detrimental autonomic and cardiovascular effects induced by central chemoreceptors activation were abolished after C1 neurons ablation in CHF rats. Neither hypoxic nor hypercapnic ventilatory chemoreflex responses were affected by DβH-SAP treatment. Our results showed that the RVLM play a pivotal role on the progression of cardiac deterioration and in the maintenance of autonomic imbalance and breathing disorders in CHF. In addition, our results showed that the sympathoexcitation and cardiac function deterioration induced by central chemoreflex activation is related to the activation of RVLM C1 neurons.

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**Poster**

**507. Cardiovascular Regulation II**

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**Program#/Poster#:** 507.14/NN22

**Topic:** F.07. Autonomic Regulation

**Support:** DFG Grant Mi1242/2-1

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**Title:** Thyroid hormones set the beat: Thyroid hormone receptors control the development of hypothalamic parvalbuminergic neurons in charge of cardiovascular function in male mice

**Authors: *L. HARDER**[1], S. DUDAZY-GRALLA[3], H. MÜLLER-FIELITZ[2], J. HJERLING LEFFLER[4], B. VENNSTRÖM[3], H. HEUER[5], J. MITTAG[1]
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**Abstract:** It is well established that proper thyroid hormone (TH) signaling is crucial for brain development and function. This becomes most evident in untreated congenital hypothyroidism leading to irreversible mental retardation, as well as in maternal hypothyroxinemia, which is associated with neurological dysfunction in the offspring causing e.g. autism. In the brain, TH actions are mainly mediated by TH receptor alpha 1 (TRα1). Consequently, mice heterozygous for the dominant-negative mutation R384C in TRα1 display extensive neuroanatomical abnormalities, including a deranged development of a parvalbumin (PV) expressing neuronal subpopulation in the anterior hypothalamic area. As these neurons centrally control blood pressure and heart rate, they constitute an important link between developmental hypothyroidism and hypertension. However, the exact orchestration of TH signaling necessary for proper development of hypothalamic PV neurons remains elusive. Using eight different mouse models with altered TH signaling during development, we unraveled the underlying molecular mechanism in great detail. Our immunohistochemical data reveal that PV neurons in the anterior hypothalamic area are GABAergic neurons with short projections remaining within the nucleus. Unlike cortical PV neurons, anterior hypothalamic PV neurons do not originate from the medial ganglionic eminences and are independent of a genetic developmental program involving Nkx2-1. Moreover, we identified a TH signaling pattern, necessary for hypothalamic PV cell development: First unliganded TRβ signaling is required until the cells become postmitotic at E12, followed by a switch to liganded TRα1 signaling until birth. Postnatally, the cells do not longer depend on TH. As previous loss-of-function studies indicated that the neurons control blood pressure and heart rate, we finally tested their involvement in the acute regulation of cardiovascular functions using chemogenic tools. In summary, our findings strengthen the connection between maternal thyroid function and offspring blood pressure control, and reveal the first clear neuroanatomical target of maternal thyroid hormone signaling. With that we add evidence on the impact of maternal thyroid disease on the offspring and the importance of routinely screening of pregnant women.

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**Poster**

**508. Gastrointestinal, Renal, Urinary, and Reproductive Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 508.01/NN23

**Topic:** F.07. Autonomic Regulation

**Title:** EFFECTS of cisplatin on the gut - brain -axis of the least shrew (Cryptotis Parva): Immunohistochemical studies using orexin R-1 receptor and serotonin

**Authors: *M. S. AL-TIKRITI**
Col. of Osteo. Med. of the Pacific/Anatomy, Western Univ. of Hlth. Sci., Pomona, CA

**Abstract:** The gastrointestinal tract (GIT) receives dual innervation by the autonomic nervous system (ANS); the sympathetic (splanchnic) and parasympathetic (vagus and pelvic spinal nerves) systems. These nerves are either excitatory (para.) or inhibitory (symp.). Vagal afferent neurons reside in nodose ganglia and are the sole primary sensory neurons that receive signals from the gut lumen to the nucleus of the solitary tract (NTS) which is densely innervated by serotonergic terminals. A third division of ANS are intrinsic to the GIT neurons called the enteric nervous system (ENS) which reside in the (Auerbach's) plexus between the inner circular and outer longitudinal muscle layer and in the submucosa (Meissner) plexus. The purpose of this study was to find out the extent of damage on the GIT and its sensory afferents caused by cisplatin. We used immunocytochemistry to detect serotonergic neurons, and orexin-1 receptors. We used nine shrews; three as controls and the remainder were injected with 10 mg/kg cisplatin (i.p.) and sacrificed 24 hours post-injection. The whole heads were demineralized with 2% formic acid for 2 weeks afterwards they were fixed with 10% neutral buffered formalin for 5 days. Samples that contained the nodose ganglia and GIT walls were processed for paraffin embedding, using standard procedure and 10 um thick sections were collected. In our previous studies; we found that cisplatin has significant impact on the GIT function indirectly via the release of several emetogenic neurotransmitters/mediators including 5-HT, substance P (SP) from the GIT enterochromaffin cells. Our current findings shows that the least shrew is similar to rats, cats and humans, by having co-localized serotonergic neurons that express OX-R1 in cells of nodose ganglia. In addition, cisplatin causes severe damage to the ganglia as manifested by shrinkage and pyknotic nuclei of the nodosal neurons. Histological examination of the GIT revealed some damage to the mucosa as shown by cellular vacuolation, exfoliation and cell death that are not only were apparent near the surface epithelium of the stomach and intestine, but also down deep close to the base of the glands. Immunohistochemical studies revealed that no 5-HT labeled cells were observed in the GIT of cisplatin treated animals compared to those of the normal gut. In conclusion, it can be deduced that cisplatin not only damages the GIT cellular elements, but also affects the neurons of the nodose ganglion, and therefore, alters the sensory stimulatory input from the GIT to brain.

**Disclosures: M.S. Al-Tikriti:** None.

**Poster**

**508. Gastrointestinal, Renal, Urinary, and Reproductive Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** F.07. Autonomic Regulation

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CONACYT 417840

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DGAPA-UNAM postdoctoral fellowship to KLG

**Title:** Multiparity impairs the electrical activity of the pelvic floor nerves in rabbits

**Authors: *K. LÓPEZ-GARCÍA**[1], S. MORENO-PÉREZ[2], R. LÓPEZ-JUÁREZ[3], R. ZEMPOALTECA[4], D. CORONA-QUINTANILLA[4], M. ROMERO-ORTEGA[5], F. CASTELAN[1], M. MARTÍNEZ-GÓMEZ[1]
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**Abstract:** Pelvic floor muscles (PFM) play supporting and functional roles for the physiology of the urogenital apparatus. It is generally assumed that damage to these muscles because the labor trauma leads to the onset of lower urinary tract disorders including urinary incontinence (UI). Scant studies, however, have been focused on the integrity of the nerves controlling PFM. To understand how multiparity affects the propagated electrical activity and morphometry of pelvic floor nerves, we aimed this work to evaluate the compound action potential (CAP) and the histological characteristics of the nerves of pubococcygeus (Pc) and bulbospongiosus (Bs) muscles in rabbits. To this end, the nerves of the Pc and Bs muscles from young nulliparous (YN) and multiparous (YM) rabbits were dissected to analyze the CAP electrophysiological recordings *in vitro*, applying electrical stimuli of variable intensity, frequency, and fixed duration (0.05 ms). Moreover, contralateral nerves were fixed to evaluate their histological characteristics. The results showed that multiparity decreased both the amplitude (3213.00 ± 641.40 vs. 1260.00 ± 127.20 mV; $P<0.05$) and the area under the curve (3001.00 ± 902.10 vs. 785.10 ± 100.90 mV*ms; $P<0.05$) of the Pc nerve CAP. The same was true for the Bs nerve in the amplitude (3193.33 ± 191.95 vs. 1760.00 ± 391.40 mV; $P<0.05$) and the area under the curve (2929.00 ± 217.50 vs. 1319.00 ± 267.70 mV*ms; $P<0.05$). Notably, multiparity did not affect any component of the CAP when measured in the EDL muscle nerve as a control. Morphometry results of the nerves suggest a classical Wallerian degeneration process in multiparas. Our present findings support that multiparity reduced the Compound Action Potential of the Pc and Bs nerves possibly due to the damage of motor axons.

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**Poster**

**508. Gastrointestinal, Renal, Urinary, and Reproductive Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 508.03/NN25

**Topic:** F.07. Autonomic Regulation

**Title:** Mechanisms for communication between the gut and brain

**Authors: *D. C. PETERSON**[1], M. LYTE[2]
[1]Physical Therapy, High Point Univ., High Point, NC; [2]Vet. Microbiology and Preventive Med., Iowa State Univ., Ames, IA

**Abstract:** Numerous studies have indicated that variations in the intestinal microflora can influence brain activity and may greatly affect various psychosis. Whether this influence is due to direct neuronal circuitry or more global systemic influences is unknown. The current study attempts to identify the mechanism by which the intestine influences brain activity by optogenetically manipulating the activity of the vagal nerve to a subsection of the jejunum. Methods: Normal mouse behavior was recorded during behavioral activities (i.e., elevated plus maze, open-field, and forced swim tests) for a period of two weeks. Mice were then surgically given 3-5 injections (0.01-0.03 µl) of either an optogenetic vector (AAV-CaMKIIa-eNpHR3.0-EYFP) or saline control into the mesenteric wall of the jejunum. During surgery the cervical vagus was identified, and a fiber optic ferrule implanted to allow illumination of the vagus nerve. After surgical recovery, behavioral tests were initiated for 2 weeks to assess variations in behavior from the initial control that may be caused by the surgery. These tests were then utilized as the control behavioral activity for each animal. Four weeks post-surgery, behavioral experiments were initiated in which vagal afferents to the injected regions of the jejunum were either deactivated with light stimulation of the vagus or in the normal (non-deactivated) state. Results were then compared for each animal. Results: Mice activity was consistent across pre-surgical control, post-surgical control, and post-surgical normal state behavioral tests. In the saline condition, animals with light activation of the vagus showed no variation in their behavioral activity from that of the other control states. In the optogenetic light deactivation condition, animal behavior was dramatically different. In each behavioral test, animals showed a freezing behavior for the extent of time that the vagus was deactivated. Within the forced swim experiments, frozen animals did not keep their head above water and tended to sink to the bottom of the tank (requiring multiple rescues during each session). Conclusions: Optogenetic deactivation of the vagal afferents of the jejunum had a dramatic and immediate influence on animal behavior. Therefore, this pathway provides an optimal mechanism by which the enteric system can influence brain activity and thus behavior.

**Disclosures: D.C. Peterson:** None. **M. Lyte:** None.

**Poster**

**508. Gastrointestinal, Renal, Urinary, and Reproductive Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 508.04/NN26

**Topic:** F.07. Autonomic Regulation

**Support:** NYS Spinal Cord Injury Research Board

CH Neilsen Foundation

NIH EB018783

**Title:** External urethral sphincter and voiding function in unanesthetized decerebrate rats

**Authors: *J. S. CARP**, T. F. FULTON
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**Abstract:** The external urethral sphincter (EUS) muscle is vital for regulating the timely passage of urine through the urethra. Past studies of anesthetized rats with intact neuraxes linked efficient voiding to phasic EUS activation (bursting). We recently published studies of EUS activity during voiding in unanesthetized unrestrained rats showing that EUS bursting was not uniformly evident during spontaneous voiding, but was consistently present four weeks after spinal transection (LaPallo et al. Neurourol Urodyn 35:696-702, 2015; LaPallo et al. J. Neurotrauma, in press). To perform physiological and pharmacological assessment of EUS function under anesthesia-free conditions, we are developing methods to record EUS electromyographic activity (EMG), bladder pressure, and urine output in unanesthetized decerebrate rats before and after intrathecal drug administration.

Female SD rats were each implanted under isoflurane anesthesia with: bilateral fine stainless steel wires in the EUS; a suprapubic catheter (PE90) in the dome of the bladder; an intrathecal catheter (PE10) after L2 laminectomy for drug administration; and a catheter (PE50) in the left carotid artery. A tube was glued to the skin surrounding the meatus to collect urine for weighing. Decerebration was performed based on the method of Dobson and Harris (Exp Physiol 97:693-8, 2012), including temporary occlusion of the right carotid artery and occlusion of the sagittal sinus with suture. After aspirating cortical tissue to expose the colliculi, the brain was transected with a scalpel and the entire forebrain was aspirated. Hemostasis was achieved using compressed sponge (Gelfoam) pieces treated with tissue adhesive (Vetbond). Isoflurane was discontinued gradually after decerebration.

The procedure was performed in rats with intact neuraxes and in rats four weeks after spinal transection. Animals that had mean blood pressures of ≥80 mm Hg after decerebration exhibited normal voiding function. EUS bursting was pronounced in the chronic spinal rats, but was less evident in intact rats. Chronic spinal rats exhibited non-voiding contractions prior to most

voiding episodes. Administration of the 5HT2A/C agonist DOI increased overall EUS EMG activity, but reduced the duration of EUS bursting, reduced voiding efficiency, and increased urine leakage.
These preliminary studies are consistent with results of our previous studies in unanesthetized freely-moving rats that EUS bursting does not always occur in intact rats but is almost always seen in chronic spinal rats. They also show the feasibility of using decerebrate rats for studying EUS function without the influence of anesthesia.

**Disclosures: J.S. Carp:** None. **T.F. Fulton:** None.

**Poster**

**508. Gastrointestinal, Renal, Urinary, and Reproductive Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 508.05/NN27

**Topic:** F.07. Autonomic Regulation

**Support:** Canadian Institute of Health and Research

Connaught Fund

Canada Foundation for Innovation

Ontario Research Foundation

IBBME Kickstarter Award

**Title:** Suppression of bladder activity following saphenous nerve stimulation in a continuous urodynamic model: A pre-clinical study

**Authors: *Z. MOAZZAM**, P. B. YOO
Inst. of Biomaterials and Biomed. Engin., Univ. of Toronto, Toronto, ON, Canada

**Abstract:** Introduction: Chronic symptoms of overactive bladder (OAB) affect nearly 18% of the world's adult population however, the current algorithm of incontinence care is modest in treatment efficacy. Recent work from our lab has shown that short-duration (10 min) electrical stimulation of the saphenous nerve (SAFN) can elicit bladder-inhibitory responses in urethane-anesthetized rats. However, it is unclear whether longer-duration trains of electrical pulses can augment the inhibitory effects of SAFN stimulation. In particular, and if so, how do urodynamic parameters alter during such bladder responses. Methods: Acute experiments were conducted in 10 urethane-anesthetized rats. The bladder dome was catheterized and connected with a pressure transducer and an infusion pump. The bladder was continuously infused with saline (0.08 ml/min) to establish a stable BCR (baseline phase). The SAFN was instrumented with a bipolar

nerve cuff electrode. The stimulation amplitude was set at 25 μA, and 40-minute stimulation trials were applied at frequencies of 10 Hz and 20 Hz. The measured basal pressure (BP), inter-contraction interval (ICI) and contraction amplitude (CA) were analyzed during both the intra-stimulation and post-stimulation periods. Each variable was normalized to the baseline of each experiment.
Results: Compared to baseline, 40 minutes of SAFN stimulation caused notable changes in each of the 3 urodynamic variables. In response to SAFN stimulation at 10 Hz (n=7), a significant increase in BP (116±6.5%) occurred during the intra-stimulation period, followed by changes in CA (70.5±8.0%) and ICI (62.1±7.2%) during the post-stimulation period. In 5 of 7 stimulation trials, we report episodes of bladder atonicity that lasted 33.0±11.3 minutes. In response to 20 Hz SAFN stimulation (n=7), there was a rapid increase in ICI (131.6%) during the initial 10 minutes, that subsequently returned close to baseline by the end of the intra-stimulation period. Significant increases in BP (124.5±10.6%) and decreases in CA (79.3±5.5%) were also observed, but the duration of bladder atonicity were markedly shorter (4.0 ± 1.2 min, 4 of 7 stimulation trials). Conclusion: The results of this study show that the duration of electrical stimulation has a significant effect on the bladder-inhibitory reflex mediated by SAFN afferents. With longer stimulation trials, we were able to observe consistently a notable upshift in the BP, reduction in the CA, and even the complete loss of voiding function for extended periods (10 Hz). Further work is needed to better understand the mechanism(s) that modulate these urodynamic variables.

**Disclosures: Z. Moazzam:** None. **P.B. Yoo:** None.

**Poster**

**508. Gastrointestinal, Renal, Urinary, and Reproductive Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 508.06/NN28

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant DK106456

NIH Grant DK052766

NIH Grant DK84567

**Title:** Mechanism of mechanosensitivity in primary intestinal enterochromaffin cells

**Authors: C. ALCAINO**[1], K. KNUTSON[1], G. YILDIZ[1], H. J. LI[2], A. B. LEITER[2], G. FARRUGIA[1], *A. BEYDER[1]
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**Abstract: INTRODUCTION:** Intestinal enterochromaffin (EC) cells are the specialized epithelial mechanosensors of the gastrointestinal (GI) epithelium that are functionally and developmentally similar to Merkel cells in the skin. EC cells release serotonin (5-HT) in response to mechanical stimuli. Recently, we discovered that human and mouse EC cells express the mechanosensitive ion channel Piezo2, but otherwise little is known about primary EC cell mechanosensitivity. **AIMS:** To characterize mouse primary EC cell mechanosensitive currents and the downstream signaling of mechanical stimulation. **METHODS:** NeuroD1 is a transcription factor important for enteroendocrine (EE) cell development. We generated a novel mouse model NeuroD1-cre::GCamP5/tdTomato in order to identify and study EE cell intracellular $Ca^{2+}$ dynamics. Immunohistochemistry was performed in colon tissues for 5-HT (EC cell marker) and chromogranin A (CgA; EE cell marker). Primary colon epithelium cultures were used for whole-cell patch clamp and $Ca^{2+}$ imaging experiments. Mechanical stimulation was performed by membrane displacement with a piezoelectrically-driven glass probe or shear flow. **RESULTS:** Immunostaining showed that 87% of all $CgA^+$ cells were $tdTomato^+$ and 85% of all $5\text{-}HT^+$ cells were $tdTomato^+$. No labeling was found outside GI epithelium. Mechanical stimulation of colon EE cells produced inward mechanosensitive currents (15.9±4.5 pA/pF, $C_m$=3.4 pF, n=4) with fast activation and inactivation kinetics (single exponential fit with $\tau_{inact}$ 11.1±2.8 ms, n=4). Current-distance relationships were fit well by Boltzmann functions, with a mid-point of 4.2±0.3 µm (n=4). The current-voltage relationship was linear crossing near 0 mV, suggesting a voltage-independent behavior (n=4). Both chemical stimulation, with 50 mM KCl ($\Delta F/F_0$ 6.3±1.2, n=6) and mechanical stimulation by shear flow significantly increased intracellular $Ca^{2+}$ ($\Delta F/F_0$ 2.3±0.7, n=3), with fast responses (time to peak 3-5 s) and return to baseline within 60 s. **CONCLUSIONS:** In the mouse colon epithelium, NeuroD1 specifically marked a high percentage of EE and EC cells. Primary colonic $NeuroD1^+$ cells had mechanosensitive currents that were inward and non-rectifying with fast activation and inactivation kinetics. Mechanical stimulation of $NeuroD1^+$ cells in primary cultures produced rapid intracellular $Ca^{2+}$ changes. These results suggest that primary EC cells have mechanosensitive ion channels with biophysical properties of Piezo2 and that mechanical stimulation of these cells elicits intracellular $Ca^{2+}$ changes, which likely precede force-induced 5-HT release. Supported by NIH DK106456, DK052766, DK84567.

**Disclosures: C. Alcaino:** None. **K. Knutson:** None. **G. Yildiz:** None. **H.J. Li:** None. **A.B. Leiter:** None. **G. Farrugia:** None. **A. Beyder:** None.

**Poster**

**508. Gastrointestinal, Renal, Urinary, and Reproductive Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 508.07/NN29

**Topic:** F.07. Autonomic Regulation

**Title:** Direct mechanism of autonomic influence on intestinal epithelial stem cell proliferation

**Authors: *E. A. DAVIS**[1], W. ZHOU[2], M. E. FELDNER[3], M. J. DAILEY[1,2]
[1]Neurosci., [2]Animal Sci., [3]Sch. of Mol. and Cell. Biol., Univ. of Illinois at Urbana-Champaign, Urbana, IL

**Abstract:** The mammalian intestinal epithelium is critical for nutrient absorption, hormone release and immune function. Stem cells located in the intestinal epithelial crypts proliferate and differentiate to produce mature cells that serve these functions. The autonomic nervous system influences intestinal epithelial stem cell proliferation. However, it is not known whether these mechanisms are direct (influencing the stem cells themselves) or indirect (acting via other cells that affect stem cell proliferation). Thus, we evaluated 1) gene expression of autonomic neurotransmitter receptors in intestinal epithelial stem cells and other crypt cells, and 2) proliferative response of intestinal epithelial organoids to application of the primary autonomic neurotransmitters *in vitro*. Briefly, small intestinal crypts were isolated from adult Lgr5+ (a stem cell marker)-GFP and wild-type mice and sorted into two populations: high GFP expression (stem cells) and low GFP expression (other crypt cells) using fluorescent activated cell sorting. Relative mRNA expression was quantified in each cell population by quantitative real time-PCR. In a separate experiment, small intestinal crypts were isolated from adult wild-type mice and grown into organoids for ten days. Organoids were treated with an autonomic neurotransmitter or a vehicle control. Proliferation was quantified using the CyQUANT NF Cell Proliferation Assay Kit at 0h, 2h, 4h and 6h after neurotransmitter administration. We found that the α2A adrenoreceptor was expressed in the stem cells and other crypt cells, and that subtypes of muscarinic acetylcholine receptors were expressed in the crypt cells. Furthermore, intestinal epithelial organoid proliferation was decreased in response to norepinephrine ($p<0.05$), but not epinephrine. These results suggest a direct mechanism for the autonomic nervous system to influence intestinal epithelial stem cell proliferation.

**Disclosures:** **E.A. Davis:** None. **W. Zhou:** None. **M.E. Feldner:** None. **M.J. Dailey:** None.

**Poster**

**508. Gastrointestinal, Renal, Urinary, and Reproductive Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 508.08/NN30

**Topic:** F.07. Autonomic Regulation

**Support:** CIHR Proof of Principle Grant

University of Toronto Connaught Innovation Award

**Title:** Effects of hypogastric nerve transection on the bladder-inhibitory reflex evoked by saphenous nerve stimulation in anesthetized rats

**Authors: *K. S. FRANZ**[1], P. B. YOO[2]
[1]Inst. of Biomaterials and Biomed. Engin., [2]IBBME, Univ. of Toronto, Toronto, ON, Canada

**Abstract: Background** It is established that reflex inhibition of bladder function can be achieved by electrically stimulating the sacral spinal nerve, pudendal nerve, and the tibial nerve in anesthetized animals. Recent work in our lab has shown that electrical stimulation of the saphenous nerve (SAFN) can also elicit bladder-inhibitory responses; however, the mechanism of this reflex is unknown. Given that the hypogastric nerve (HGN) modulates bladder function and projects to similar lumbar spinal regions as the SAFN in rats, we hypothesized that the bladder-inhibitory effects of SAFN stimulation involve a spinal-mediated mechanism. In this study, we investigated the effects of bilateral HGN transection on the bladder-inhibitory effects of SAFN stimulation.
**Methods** Acute experiments were conducted in 11 urethane-anesthetized rats (250-300g, female), where the effects of bilateral HGN transection on SAFN stimulation were tested in the same (n=4) or in separate (n=7, 3 post-transection rats) animals. Using a surgically implanted suprapubic catheter, the bladder was infused continuously with 0.1% acetic acid (AA). Following 60-minute baseline period, changes in bladder function were measured in response to 40-minute stimulation trials applied at 10 Hz and at amplitudes of 50 µA and 100 µA. Electrical pulses were delivered via a bipolar nerve cuff electrode placed around the SAFN. Bilateral HGN transection was performed caudal to the inferior mesenteric ganglion.
**Results** Bladder atonicity, characterized by loss of bladder activity and urethral sphincter muscle bursting, was observed in response to SAFN stimulation trials applied at 50 µA and 100 µA. In rats where SAFN stimulation was tested in the same animal (n=4), atonic bladder episodes occurred in 1 of 4 rats before HGN transection, but in 3 of 4 rats after HGN transection. These episodes lasted 10.6 minutes and 11.6 ± 4.0 minutes, respectively. In rats where SAFN stimulation was tested in separate animals (n=7), bladder inhibition periods occurred in 1 of 4 rats with HGN intact, but in 2 of 3 rats with HGN transected. The duration of these episodes was 7.0 minutes and 45.2 ± 24.4 minutes, respectively.
**Conclusion** The increased incidence of SAFN-mediated episodes of bladder atonicity following HGN transection (25% pre-transection vs. 71% post-transection) suggest that the absence of the sympathetic pathway enhances the bladder-inhibitory effects of SAFN stimulation in AA-infused rats. Further work is needed to better characterize the precise role of the HGN during SAFN stimulation.

**Disclosures: K.S. Franz:** None. **P.B. Yoo:** None.

**Poster**

**508. Gastrointestinal, Renal, Urinary, and Reproductive Regulation I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 508.09/NN31

**Topic:** F.07. Autonomic Regulation

**Support:** University of Toronto Connaught Fund

**Title:** Changes in bladder capacity and voiding efficiency estimated during continuous-fill cystometry in anesthetized rats that are provided with tibial nerve stimulation

**Authors: *J. P. PAQUETTE**[1], P. B. YOO[1,2]
[1]Inst. of Biomaterials & Biomed. Engin., [2]Edward S. Rogers Sr. Dept. of Elec. & Comp. Engin., Univ. of Toronto, Toronto, ON, Canada

**Abstract:** Although the precise therapeutic mechanism is unknown, tibial nerve stimulation (TNS) is used clinically to treat symptoms of overactive bladder. Recent preclinical studies show that TNS can evoke significant bladder-inhibitory responses that persist beyond the period of electrical stimulation, by changes in bladder capacity (BC) and the inter-contraction interval (ICI). However, there is limited knowledge of the effects of TNS on urodynamic parameters that characterize voiding function, which include voided volume, post-void residual, and voiding efficiency (VE). The goal of this study was to characterize changes in urodynamic function that result from TNS during continuous-fill cystometry. Non-survival experiments were conducted in urethane-anesthetized Sprague-Dawley rats (280 - 316 g, n = 3, female) instrumented with a suprapubic bladder catheter. A stimulating bipolar nerve cuff electrode was implanted on right tibial nerve, and a pair of wire electrodes were inserted into the right foot. Rats were placed in a prone position, where a force-displacement transducer was positioned to collect fluid excreted from the urethral meatus. The study protocol involved continuous infusion of saline into the bladder (0.05 mL/min). Following an initial baseline period (90 minutes), TNS was applied for 30 minutes (6T, 10 Hz) and post-stimulation effects were measured for 30 minutes. The post-void residual bladder volume was measured at the end of each experimental trial to estimate the BC and VE of every bladder void using the recursive mass balance equation of the bladder. Compared to baseline, TNS resulted in negligible changes in the BC (1.5 ± 5.8%) and ICI (-0.2 ± 0.8%) during the intra-stimulation period. In contrast, notable increases in both variables - 17.1 ± 15.9% and 34.0 ± 4.6%, respectively - were observed during the post-stimulation period. These results are consistent with the bladder-inhibitory effects of TNS. Interestingly, despite the inhibitory effects of TNS, we also observed apparent increases in the VE, particularly during the post-stimulation period (10.8 ± 14.4%). The preliminary results of this study confirm the bladder-inhibitory effects of TNS (i.e., increased BC and ICI), and also show a concomitant

increase in the VE. Further work is needed to understand the potential role of these physiological variables in the therapeutic effects of TNS in patients.

**Disclosures: J.P. Paquette:** None. **P.B. Yoo:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.01/NN32

**Topic:** F.07. Autonomic Regulation

**Support:** NIBIB U18EB021760

**Title:** Real-time estimation of bladder pressure through dorsal root ganglia recordings in an overactive bladder model

**Authors: *A. OUYANG**, T. M. BRUNS
Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

**Abstract:** Overactive bladder patients often suffer from incontinence and a frequent urge to urinate. Previous studies have established electrical stimulation at various locations in the peripheral nervous system to improve continence. However, continuous stimulation facilitates habituation of neural pathways and consumes battery power. Sensory feedback-based stimulation may offer greater clinical benefit by driving bladder function only when necessary. In this study, we use sacral-level dorsal root ganglia (DRG) as a recording site to monitor the bladder state. We acquired neural recordings from microelectrodes in S1 and S2 DRG during acute alpha-chloralose anesthetized feline procedures and monitored bladder pressure. During each trial, 0.5% acetic acid in saline was infused at 2ml/min until leaking was observed. Overactive bladder was confirmed by observing a lower volume threshold for voiding and increased bladder activity. A Kalman filter was used to establish a training model for estimating bladder pressure from thresholded DRG neural activity (training). This model was then applied to neural data from a bladder fill in real-time to estimate the pressure (testing). The bladder pressure was estimated every 2 seconds, using 9 recording channels and a firing rate normalization method. In a pilot study, we were able to decode bladder pressure with a 10% normalized root mean squared error (NRMSE), and a correlation coefficient (CC) of 0.98 for a 15 minute infusion trial. Subsequent offline analysis using the training model established from a saline-only bladder fill and tested on an overactive-model bladder fill, yielded an accurate estimation (NRMSE of 7% and a CC of 0.96). Reversing the training and testing order yielded similar performance (NRMSE of 14% and CC of 0.96). The relationship between the bladder pressure and the multiunit firing rates from channels used in the estimations changed minimally between the healthy and overactive bladder

models. This result suggests the potential of using decoded sensory feedback to define control signals for a closed-loop bladder neural prosthesis, in a dysfunctional bladder state.

**Disclosures: A. Ouyang:** None. **T.M. Bruns:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.02/NN33

**Topic:** F.07. Autonomic Regulation

**Title:** Evaluating neurogenic oscillations in vaginal blood perfusion as a genital sexual arousal response to peripheral nerve stimulation in anesthetized female rats

**Authors: *L. L. ZIMMERMAN**[1,2], I. C. RICE[1,2], M. B. BERGER[3], T. M. BRUNS[1,2]
[1]Biomed. Engin., [2]Biointerfaces Inst., Univ. of Michigan, Ann Arbor, MI; [3]Obstetrics and Gynecology, Univ. of Michigan Hlth. Syst., Ann Arbor, MI

**Abstract:** The aim of this research is to determine the effects of pudendal and tibial nerve stimulation on the genital sexual arousal of an anesthetized female rat through analysis of neurogenic oscillations in vaginal blood perfusion. Female sexual dysfunction (FSD) is a condition which can include deficits in desire, arousal, orgasm, and lubrication. FSD affects between 40-45% of sexually active women, yet there are limited treatment options. In clinical studies involving sacral neuromodulation (SNM) and percutaneous tibial nerve stimulation (PTNS) for bladder dysfunction, female patients sometimes note an additional positive impact on sexual function. Few prior studies have examined this effect preclinically, and there is no standard method for evaluation of genital arousal. We have shown the ability to elicit increases in vaginal blood perfusion with peripheral nerve stimulation as shown by changes in laser Doppler flowmetry (LDF) signals from the vaginal wall. Previous studies in unrelated applications have segmented the frequency contributions of LDF signals into different sources, including neurogenic sources. The neurogenic range of tissue perfusion oscillations is from 0.076-0.200 Hz, and any changes in this range suggests modulation by the autonomic nervous system. This frequency range also eliminates the impact of DC drift, respiration artifacts, and bladder contraction artifacts on signal analysis. In this study, we propose to evaluate increases in neurogenic oscillations as an indicator of peripheral nerve stimulation-driven genital sexual arousal. In anesthetized female rats, we isolated and stimulated the pudendal or tibial nerve unilaterally for thirty minutes. The stimulation frequency was between 5-40 Hz with an amplitude that was 2-4 times the threshold for causing a distal muscle response. Vaginal blood perfusion was measured with LDF as the primary proxy for arousal, with changes in the neurogenic frequency range assessed with wavelet analysis. Significant increases in the energy of neurogenic oscillations is a proxy for genital sexual arousal. Across experiments, 6/8 pudendal

nerve and 12/15 tibial nerve procedures had increases in the neurogenic frequency range. This research demonstrates that analysis of the neurogenic power in LDF signals provides a novel approach for assessing genital arousal responses. Furthermore, these results suggest that peripheral nerve stimulation may be utilized as a treatment for FSD.

**Disclosures: L.L. Zimmerman:** None. **I.C. Rice:** None. **M.B. Berger:** None. **T.M. Bruns:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.03/OO1

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant 1U18EB021760-01

**Title:** Detecting bladder afferent activity from the surface of sacral dorsal root ganglia with a non-penetrating thin-film electrode array

**Authors: *Z. J. SPERRY**[1,2], K. NA[3], S. S. PARIZI[3], H. J. HILOW[1,2], J. P. SEYMOUR[3], E. YOON[3], T. M. BRUNS[1,2]
[1]Biomed. Engin., [2]Biointerfaces Inst., [3]Electrical Engin. and Computer Sci., Univ. of Michigan, Ann Arbor, MI

**Abstract:** In this work, we demonstrate the ability of a thin-film non-penetrating electrode array to record bladder afferent activity from the surface of sacral dorsal root ganglia (DRG). Sacral DRG contain cell bodies for lower urinary tract afferents from the pelvic and pudendal nerves. Interfacing with the DRG could allow for closed-loop neural control of bladder function. In order to overcome the limitations of penetrating electrode arrays, we have developed a flexible polyimide electrode array with iridium electrode sites. This array interfaces with the DRG surface without penetrating the epineurium. We have previously demonstrated the ability of this array to detect cutaneous afferent neural activity, but this is the first report of recording bladder afferent activity from the surface of DRG. Under isoflurane anesthesia, we exposed the lumbosacral DRG of cats and placed a suprapubic bladder catheter for infusion and pressure monitoring. Under alpha-chloralose anesthesia, we placed the array on the surface of a DRG, noting its relative location, and infused room temperature saline into the bladder in 5 mL boluses to a volume of 30 mL. We recorded electrical signals at the DRG surface at 30 kHz using a Ripple Grapevine system. Electrode potentials were high-pass filtered offline with a cut-off of 250 Hz and noise floor threshold crossings times were determined using Plexon Offline Sorter. Finally, we calculated threshold crossing frequency and correlated this firing rate with bladder pressure. Multiple channels on an S2 placed array had firing rates which were highly correlated

with bladder pressure (max correlation: 0.82). 6-8 channels with bladder afferents were identified in each trial, usually clustered on closely-spaced electrode sites used as tetrodes (25 μm pitch). Activity was also identified in the same and other electrode placements corresponding to pudendal and somatic afferents, with spatial differences suggesting somatotopy. These results support our ultimate goal of interfacing chronically with sacral DRG to study bladder neurophysiology and providing closed-loop control toward a neuroprosthetic system.

**Disclosures: Z.J. Sperry:** None. **K. Na:** None. **S.S. Parizi:** None. **H.J. Hilow:** None. **J.P. Seymour:** None. **E. Yoon:** None. **T.M. Bruns:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.04/OO2

**Topic:** F.07. Autonomic Regulation

**Support:** University of Michigan MCubed Pilot Grant

**Title:** Kilohertz frequency electrical stimulation on renal nerves increases urine glucose excretion

**Authors: *A. A. JIMAN**[1,2], A. G. LEWIS[3], K. H. CHHABRA[4], P. S. CEDERNA[1,3], R. J. SEELEY[3], M. J. LOW[4], T. M. BRUNS[1,2]
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**Abstract:** Over 400 million people around the world are affected by diabetes. Many diabetic patients struggle with glycemic control and are in high risk of morbidity and mortality. In recent years, the role of the kidney in glucose homeostasis has gained considerable interest. Kidneys are innervated by renal nerves, and renal denervation animal models have shown improved glucose regulation associated with increased urine glucose excretion. We hypothesize that stimulation of renal nerves at high frequencies (5-50 kHz), which can block propagation of action potentials, will increase urine glucose excretion. In this study, the left kidney of male rats was exposed through a midline abdominal incision. A nerve cuff electrode was placed on the renal artery, encircling renal nerves that run along the artery. Both ureters were cannulated to obtain urine samples from each kidney independently. Renal nerves were electrically stimulated (10-50 kHz, 15 V) for 25 minutes, and two minutes into stimulation, a glucose dose (1 g) was administered through the jugular vein. Urine samples were collected at 5-minute intervals, and colorimetric assays were used to quantify the amount of glucose excreted. In two trials of 33 kHz stimulation, the stimulated kidney showed an increase of 6.2 ± 13.8% in accumulated urine glucose excretion and an average of 11.6 ± 5.6% increase in urine glucose concentration with respect to the non-

stimulated kidney. In a single trial of 50 kHz stimulation, the stimulated kidney showed an increase of 24.6% in accumulated urine glucose excretion and an average of 18.9% increase in urine glucose concentration. In separate experiments, renal artery blood flow (mL/min) and kidney perfusion (laser speckle contrast imaging) were measured during nerve cuff stimulation. Electrical stimulation at 10, 50 and 100 kHz showed a small decrease of 4.6%, 1.3% and 3.2% in renal artery blood flow, respectively. Furthermore, we observed a minimal decrease of 0.9% and 1.9% in kidney perfusion at 33 and 50 kHz, respectively. Stimulation at 10 Hz is known to cause glomerular ischemia with kidney surface whitening. We recorded a decrease of 30.7% in renal artery blood flow and 53.1% in kidney perfusion at 10 Hz stimulation. Overall, our results show that kilohertz frequency electrical stimulation on renal nerves is a possible approach for the modulation of urine glucose excretion, with minimal effect on renal blood flow. This study suggests that electrical stimulation on renal nerves is a potential treatment modality for glycemic control.

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**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.05/OO3

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant TR01 NS081707

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McDonnell Center for Cellular and Molecular Neurobiology Postdoctoral Fellowship

**Title:** Optogenetic manipulation of bladder function

**Authors: *A. D. MICKLE**[1], P. SRIVASTAVA[2], V. K. SAMINENI[2], H. LAI[3], R. W. GEREAU, IV[4]
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**Abstract:** Millions of people in the United States suffer from bladder dysfunction and pain caused by interstitial cystitis/bladder pain syndrome and overactive bladder. The underling pathologies for many of these diseases are poorly understood, however it has been demonstrated that sensory nerve fibers play an integral role in many of these diseases. Our lab has been studying the role of these sensory nerve fibers in bladder physiology and pathophysiology using optogenetics. Optogenetics is a powerful tool that can be used to specifically manipulate

neuronal activity using light activated channels and pumps. To better understand the role of bladder afferents in bladder diseases, we have developed multiple approaches using viruses and mouse genetic lines to express opsins in bladder sensory neurons to modulate neuronal activity. We have demonstrated effective delivery of opsins to bladder afferents using intraganglionic injections of adeno associated viral vectors, which produces prolonged, stable expression. However this approach does not restrict expression of the light-sensitive proteins to the bladder, so focal illumination of the bladder is necessary to achieve bladder-specific optogenetic manipulations. We have also found that bladder wall injections of the retrograde herpes simplex viral vectors can achieve short term, bladder afferent-specific expression of opsins. We demonstrate with both approaches that activation of the excitatory opsin channelrhodopsin-2 (ChR2) leads to the initiation of bladder contraction, whereas activation of the inhibitory opsin archaerhodopsin (Arch) results in the delayed contractions. Using genetically engineered mouse lines, we can restrict the expression of these opsins to specific subtypes of bladder afferents. We did this by crossing mice that express Cre recombinase-dependent ChR2 or Arch with mice that express cre recombinase in Nav1.8-expressing neurons, resulting in Nav1.8-ChR2 and Nav1.8-Arch mice. Optogenetic activation of bladder afferents in Nav1.8-ChR2 mice initiated bladder contractions, while inhibition bladder afferents in Nav1.8-Arch mice prolonged cystometric contractions. Altogether, we show that both virally delivered and genetically expressed opsins can be used to bidirectionally modulate and manipulate bladder function. Restriction of opsin expression to other sub-populations of bladder afferents could lead to a better understanding of the role of various afferent populations in bladder function and disease.

**Disclosures:** **A.D. Mickle:** None. **P. Srivastava:** None. **V.K. Samineni:** None. **H. Lai:** None. **R.W. Gereau:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurolux.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.06/OO4

**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant NINDS NS070267

**Title:** Determining integrity of bladder innervation and smooth muscle function after long-term lower spinal cord injury

**Authors: *D. M. SALVADEO**[1], M. F. BARBE[1], N. FRARA[1], E. TIWARI[3], A. S. BRAVERMAN[1], M. MAZZEI[2], A. ROBERTS[1], M. R. RUGGIERI, Sr.[1,3]
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**Abstract:** The impact of autonomic nerve injury on smooth muscle is not well understood. We explored the integrity of bladder innervation and smooth muscle function after lower spinal cord injury. The bladders of female canines were surgically decentralized by bilateral transection of all spinal roots caudal to L7, including the dorsal root of L7. Video surveillance of housing cages allowed measurement of the frequency and duration of urination postures at monthly intervals post operatively (PO). Retrograde labeling of pelvic plexus neuronal cell bodies was quantitated from Fluorogold (FG) injected near the ureterovesical junction 3 weeks before euthanasia. Functional integrity of pelvic plexus-bladder innervation was determined by electrical stimulation of the pelvic plexus immediately prior to euthanasia. Bladder caspase-3 immunostaining for cellular apoptosis was quantified to confirm integrity. Micturition postures were observed in only 2/6 animals by 2 months PO and 3/6 by 4 months PO while postures remained intact in sham animals, confirming that decentralization reduces sensation of bladder fullness. The ability of 3/6 animals to sense bladder fullness at 4 months PO may be from sensory nerve sprouting or variations in the bladder sensory innervation. The pelvic plexus maintained its ability to induce *in vivo* bladder contractions a year after spinal cord injury, although sacral root transection significantly decreased maximal bladder contraction. Abundant FG-labeled neuronal cell bodies were observed in ganglia in the pelvic plexus of both sham and decentralized animals demonstrating that the ganglia remain intact up to 6 months after injury despite sensory losses. Immunohistochemical stain for caspase-3 showed no difference across groups, suggesting no increase in apoptotic cell death. Smooth muscle contractility is preserved across groups after *in vitro* nerve-evoked stimulation, indicating that the intramural nerves and smooth muscle of the bladder are intact up to 12 months after injury and therefore, nerve reinnervation strategies could be successful.

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**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

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**Program#/Poster#:** 509.07/OO5

**Topic:** F.07. Autonomic Regulation

**Support:** NIH 1R01NS070267

**Title:** Monitor selective nerve activity during bladder filling in canines

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**Abstract:** We sought to develop methods for monitoring nerve activity during bladder filling in normal intact bladders, methods that we would eventually use for monitoring effectiveness of sensory reinnervation of the bladder after decentralization and rerouting nerve transfer. Electrophysiology studies were designed to perform nerve stimulation and recording in rats and canines. Animals were anesthetized using isoflurane (3-5% induction dose inhalation). Electroneurogram (ENG) recordings were performed using a bipolar cuff electrode: 1) in rats, from sciatic nerves (n=7) during hind paw stimulation with Semmes-Weinstein monofilaments of varying forces (10g-300g) and, 2) in rats and canines, from hypogastric nerves (n=7 each) during bladder filling. Recordings included electrical stimulation (0.2-10mA, 20Hz) of the hind paw or hypogastric nerve and were performed using a low noise amplifier at 10k gain, sampled at 20kHz, filtered at 300Hz-10kHz. Data was converted from analog to digital and then captured using LabChart software (ADInstruments, CO). Also, maximum changes in detrusor pressures were determined after electrical stimulation of the hypogastric nerves prior to recording. We found in rats that sciatic nerve recordings consistently showed increased afferent fiber discharge with increased size of the monofilament used to stimulate the hindpaw. In contrast, recording from bladder nerves showed that combined afferent and efferent discharges increased substantially in response to bladder filling in 2 of 7 rats, and increased moderately in 2 rats. However, there was no response in the remaining 3 rats, perhaps due to nerve damage during cuff placement. In canines, we found hypogastric nerve activity decreased substantially in response to bladder filling in 1 of 7 dogs, and increased moderately in one dog, and showed no response in the remaining 5 dogs. While we need to improve our technique in canines, based on results from sciatic nerve and hypogastric nerve recordings in rats, our technique may be appropriate for recording afferent nerve activity during bladder filling in animals with surgically rerouted neural pathways.

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**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.08/OO6

**Topic:** F.07. Autonomic Regulation

**Support:** Galvani Bioelectronics

NIDDK K12 DK100024

**Title:** State-dependent stimulation of the pudendal nerve increases bladder capacity and voiding efficiency

**Authors: *J. A. HOKANSON**[1], C. L. LANGDALE[1], A. SRIDHAR[5], P. H. MILLIKEN[5], W. M. GRILL[1,2,3,4]
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**Abstract:** Overactive bladder (OAB), resulting in urgency, frequency, and incontinence, is a highly prevalent condition that leads to medical complications and decreased quality of life. Many persons fail to find therapeutic relief from currently available treatments.
Pudendal nerve stimulation is a promising alternative therapy that is not currently in clinical use. Pudendal nerve stimulation produces increases in bladder capacity in animal models as well as in limited human testing. As well, activity in pudendal nerve afferents, particularly urethral afferents, promotes bladder emptying. By using different stimulation parameters, stimulation of the pudendal nerve may promote differentially bladder filling and efficient voiding. Strong inhibition of the bladder to promote continence can treat incontinence but may reduce voiding efficiency, and some patients exhibit both poor bladder filling and poor voiding (e.g., detrusor hyperactivity with impaired contractility).
We hypothesized that state-dependent stimulation of the pudendal nerve would increase both bladder capacity and voiding efficiency in rat and cat models.
In urethane-anesthetized female Wistar rats, the sensory branch of the pudendal nerve was stimulated during cystometry. In initial experiments, Prostaglandin E2 was administered intravesically as a model of OAB. In three of four experiments, high amplitude stimulation increased bladder capacity, which when followed by low amplitude stimulation, just prior to and during voiding, improved voiding efficiency (n=2), or rescued a bladder contraction from overflow incontinence (n=1) compared to trials without stimulation and trials with stimulation only during bladder filling.
State-dependent stimulation was also investigated in two alpha-chloralose anesthetized male cats. The compound pudendal or sensory pudendal (i.e. dorsal nerve of the penis or DNP) nerve was stimulated to increase bladder capacity. Upon initiation of micturition, this initial stimulus was terminated and replaced by stimulation of the motor branch in a bursting pattern, or stimulation of the DNP using a different pattern than that used during filling, to promote voiding. In both cat experiments state-dependent stimulation improved both bladder capacity and voiding efficiency.
These findings suggest that state-dependent stimulation of the pudendal nerve may be a promising approach to maximize both bladder capacity and voiding efficiency.
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**Disclosures:** **J.A. Hokanson:** 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.; Galvani Bioelectronics. **C.L. Langdale:** 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.; Galvani Bioelectronics. **A. Sridhar:** A. Employment/Salary (full or part-time):; Galvani Bioelectronics. **P.H. Milliken:** A. Employment/Salary (full or part-time):; Galvani Bioelectronics. **W.M. Grill:** 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.; Galvani Bioelectronics.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.09/OO7

**Topic:** F.07. Autonomic Regulation

**Support:** Galvani Bioelectronics, UK.

**Title:** Voiding behavior in awake unrestrained untethered spontaneously hypertensive and control rats

**Authors: *C. L. LANGDALE**[1], J. HOKANSON[1], P. MILLIKEN[5], W. GRILL[1,2,3,4]
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**Abstract:** Overactive bladder (OAB), resulting in urgency, frequency, and incontinence, is a highly prevalent condition that leads to medical complications and decreased quality of life. There are several animal models used to investigate the mechanisms of and treatments for OAB. In particular, the spontaneously hypertensive rat (SHR) is a genetic model of hypertension that also exhibits symptoms of OAB that include detrusor overactivity, increased frequency, and decreased bladder capacity and voided volume. While most prior studies were conducted in awake unrestrained rats, they employed catheters implanted in the bladder and tethered to an infusion pump and artificial bladder filling. The purpose of our study was to 1) monitor voiding behavior in awake unrestrained untethered age-matched SHR and control rats, and 2) successfully record bladder pressure and external urethral sphincter (EUS) function in telemetry (TTY) implanted awake unrestrained untethered SHR and control rats. Food and water consumption, body weight, voiding frequency (VF), and voided volume (VV) were recorded. Each rat was placed in a metabolism cage for 23-24 hours per day, up to twice a week. For telemetry (TTY) implanted animals, a pressure catheter was implanted into the dome of the bladder, and a bipolar paddle electrode was inserted between the urethra and pubic symphysis to record bladder pressure (BP) and external urethral sphincter (EUS) electromyogram (EMG). The SHRs body weight, food, and water consumption were decreased compared to controls. However, after normalizing for body weight, no differences in food or water consumption were observed. Controls exhibited a diurnal pattern in their voiding behavior, consisting of larger VV

with decreased VF during sleep cycles and smaller VV with increased VF during awake cycles. SHRs voided less volume less frequently compared to controls; however, no difference in VF was observed after normalizing for water consumption. Additionally, no diurnal voiding pattern was noted in the SHRs (VV was similar during the awake and sleep cycles). BP and EUS EMG activity were successfully recorded in TTY implanted awake unrestrained untethered rats. High frequency osciilations in BP coincided with EUS EMG bursting during voiding. Our results confirm previously reported decreases in VV. However, the lack of increased VF suggests that artificial filling during awake cystometry may alter normal voiding behavior. Further, TTY implanted rats with BP and EUS EMG is a promising approach to understand voiding behavior in awake unrestrained untethered rats.

**Disclosures: C.L. Langdale:** 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.; Galvani Bioelectronics. **J. Hokanson:** 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.; Galvani Bioelectronics. **P. Milliken:** A. Employment/Salary (full or part-time):; Galvani Bioelectronics. **W. Grill:** 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.; Galvani Bioelectronics.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.10/OO8

**Topic:** F.07. Autonomic Regulation

**Support:** 4K12DK100024-04

**Title:** Nerve stimulation increases voiding efficiency in a novel model of detrusor underactivity

**Authors: *E. J. GONZALEZ**, W. M. GRILL
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**Abstract:** Detrusor underactivity (DUA) is an understudied health concern that affects up to 45% of men and women. The clinical management of DUA is inadequate and fails to improve the quality of life of these patients. The limited availability of animal models that exhibit the integrated pathophysiology of DUA impedes the development of new therapeutic approaches. The current studies characterized the bladder function of an obesity model of DUA and investigated neuromodulation as a management option to restore efficient bladder emptying.

Eight-week old female obese-prone (OP) and obese-resistant (OR) rats were purchased from Charles River (Boston, MA). Experimental procedures were approved by the Duke University IACUC. OP and OR rats were fed a 45% fat diet (Research Diets, Inc.) from 9-21 weeks and a 60% fat diet (Research Diets, Inc.) from 21-24 weeks. Serum was collected from the tail vein for metabolic analysis at 8 and 24 weeks. At 24 weeks, OP and OR rats were anesthetized with urethane (1.2 g/kg s.c., supplemented as needed). The bladder was exposed and a flared PE-60 catheter was inserted into the bladder dome. The catheter was secured and connected via a 3-way stopcock to a pressure transducer and infusion pump. A paddle with platinum iridium contacts was placed between the pubic symphysis and the EUS to record EMG signals. A bipolar micro-cuff (CorTec, Germany) was also placed around the motor or sensory branch of the pudendal nerve or the pelvic nerve for electrical stimulation. Pressure and EMG signals were amplified, filtered, and sampled. Following diet-induced obesity (DIO), OP rats weighed more than OR rats and had normal blood glucose but developed hyperinsulinemia and hypertriglyceridemia. OP rats exhibit DUA and urinary retention following DIO. Compared to OR rats, OP rats had increased volume threshold, decreased peak micturition pressure ($16.6 \pm 1.2$ vs. $23.9 \pm 1.1$ $cmH_2O$, $p \leq 0.001$), decreased voiding efficiency ($8.4 \pm 2.2$ % vs. $40 \pm 5.2$ %, $p \leq 0.0001$), and decreased EUS EMG activity during voiding. Patterned electrical stimulation of the motor branch of the pudendal nerve increased voiding efficiency two-fold in OP rats ($11 \pm 5.8$ % vs. $22 \pm 6.3$ %, $p \leq 0.05$), whereas, stimulation of the sensory branch of the pudendal nerve did not alter voiding efficiency. OP rats also had no change in voiding efficiency and decreased evoked contraction amplitude with electrical stimulation of the pelvic nerve. This animal model may be used to understand the pathophysiology of DUA and establish the efficacy of neuromodulation to recover efficient bladder emptying with urinary retention.

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**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

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**Program#/Poster#:** 509.11/OO9

**Topic:** F.07. Autonomic Regulation

**Support:** NIH-NINDS NS070267

**Title:** Localization of neuromuscular nicotinic receptors in the functionally reinnervated canine bladder after prolonged decentralization

**Authors: N. F. FRARA, 19140-5104**[1], A. S. BRAVERMAN[1], D. M. SALVADEO[1], E. TIWARI[3], A. ROBERTS[1], M. F. BARBE[4], *M. R. RUGGIERI, SR[2]
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Philadelphia, PA; [3]Electrical and Computer Engin., Temple Univ., Philadelphia, PA; [4]Anat. and Cell Biol., Temple Univ. Sch. of Med., Philadelphia, PA

**Abstract:** We have previously found that succinylcholine, a depolarizing neuromuscular nicotinic receptor blocker, prevents bladder contraction induced by new neuronal pathways established by nerve transfer in decentralized dogs. Here, we studied detrusor pressure response *in vivo* and contractile response of bladder smooth muscle strips *in vitro* from sham, decentralized and reinnervated animals to localize neuromuscular nicotinic receptors involved. Three groups of female hound dogs (5/group) were used: sham, 12-month decentralized and 6-month reinnervated. Decentralization was performed by bilateral transection of all spinal roots caudal to L7, including dorsal roots of L7 and hypogastric nerves. Reinnervation was created by bilateral transfer of obturator nerves to anterior vesical branches of pelvic nerve. Two-way ANOVAs and Sidak post-hoc tests determined group differences. In reinnervated dogs, neuromuscular nicotinic receptor blockade with intravenous atracurium besylate reduced increased detrusor pressure induced by electrical stimulation of upper lumbar nerve roots. Atracurium did not block sacral nerve root stimulation induced pressure in sham-operated controls. *In vitro*, 5 μM atracurium had no effect on nerve evoked contractions in any experimental group. Neither the competitive neuromuscular nicotinic receptor antagonist d-tubocurarine nor the ganglionic antagonist hexamethonium inhibited electric field stimulation (EFS)-induced contractions of reinnervated or sham-operated control bladder strips. 1 μM tetrodotoxin (TTX) blocked contractile response in all groups. Similarly, EFS-evoked contractions were strongly reduced by 10 μM alpha, beta-methylene ATP (α,β-mATP) and 1 μM atropine in all groups. *In vivo* blockade of nerve-evoked bladder pressure by atracurium in reinnervated, but not sham operated controls, suggests that neuromuscular nicotinic receptors mediate bladder contractions induced by upper lumbar stimulation. Because neither atracurium nor d-tubocurarine blocked in-vitro contractions induced by EFS in reinnervated bladders, the neuromuscular nicotinic receptors involved in the neuronal pathways originating from the upper lumbar spinal cord must not be located in bladder muscle or intramural ganglia; they may be located in pelvic plexus ganglia or in the spinal cord. TTX blockade validates that EFS-induced contractions at all frequencies were nerve-evoked. The response to blockade of nerve evoked muscle strip contractions with a combination of atropine and α,β-mATP, indicates that both muscarinic and purinergic components account for virtually all nerve mediated responses.

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**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

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DoD/CDMRP W81XWH-14-1-0605

**Title:** Spinal dopamine receptors continue regulating the recovered urinary function in rats following complete spinal cord transection

**Authors: *S. HOU**[1], H. SHARIF[1], S. L. DAUGHERTY[2], J. H. DEFINIS[1], W. C. DE GROAT[2]
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**Abstract:** Lower urinary tract (LUT) function is controlled by multiple neuronal mechanisms at both supraspinal and spinal levels that synchronize bladder and external urethral sphincter (EUS) activity. Recently, we discovered that dopamine (DA) is synthesized in the rat spinal cord and regulates bladder function after a spinal cord injury (SCI) interrupts spinobulbospinal reflex pathways. To fully understand the spinal endogenous DA-ergic machinery in the recovered micturition, we used metabolic cages to measure spontaneous voiding, and employed bladder cystometry and EUS electromyography (EMG) combined with different DA receptor (DR) agonists or antagonists to examine urodynamic responses in unanesthetized SCI rats. Three weeks after complete SCI at the 10$^{th}$ thoracic level, involuntary micturition was reestablished due to the reorganization of spinal reflex circuitry. Subcutaneous delivery of L-DOPA (30 mg/kg), a DA precursor, together with carbidopa (3 mg/kg) decreased spontaneous voiding frequencies and increased voiding volumes. During cystometry and EMG assay, injection of L-DOPA (1-30 mg/kg) in combination with carbidopa (0.1-3 mg/kg) intravenously (iv) decreased the amplitude of bladder contractions and the frequency of non-voiding contractions, and reduced EUS tonic activity but increased the duration of EUS bursting phase, leading to better coordinated detrusor and EUS activity. Apomorphine (1-300 μg/kg, iv), a non-selective DR agonist, enhanced the amplitude of bladder contractions and EUS bursting duration and suppressed EUS tonic activity. Similarly, quinpirole (10-300 μg/kg, iv), a selective $DR_2$ agonist, also increased bladder activity and EUS bursting but decreased EUS tonic activity. A specific $DR_2$ antagonist remoxipride (0.1-3 mg/kg, iv) reversed the effects of quinpirole but when administered alone, it only had minimal effects on bladder and EUS activity. This indicates that the activation of spinal $DR_2$ facilitates voiding. On the other hand, administration of SKF38393 (0.1-3 mg/kg, iv), a selective $DR_1$ agonist, increased tonic EUS activity; while a $DR_1$ antagonist SCH23390 (0.01-1 mg/kg, iv) also increased EUS tonic activity. However, the latter occurred during a period of large spastic movements of the body and legs which made the effects of the drug difficult to evaluate. Thus, spinal DA modulates bladder and EUS activity via distinct receptors: $DR_1$ are more involved in activation of the EUS and urine storage whereas $DR_2$ are more involved in bladder activation,

EUS bursting and voiding. Pharmacological manipulation of spinal DR or DA levels may become a therapeutic strategy to improve LUT functional recovery following SCI.

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**Poster**

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**Title:** Systemic blockade of proNGF/p75 signaling improves urinary bladder function in mice with complete spinal cord injury (SCI)

**Authors: *M. A. VIZZARD**[1], K. TOOKE[1], S. MALLEY[1], N. GANESH[2], F. FARHADI[2], J. C. RYU[2], S. O. YOON[2]
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**Abstract:** SCI rostral to the lumbosacral spinal cord results in detrusor sphincter dyssynergia and neurogenic detrusor overactivity producing highly inefficient voiding. Impaired bladder emptying, resulting in urinary retention with high bladder pressure, is a major problem for SCI individuals. Effective drug treatments do not exist. NGF/receptor interactions contribute to bladder dysfunction after SCI, in OAB and with IC/PBS. Of the NGF receptors, TrkA and p75, p75 is more relevant under pathological conditions, inducing apoptosis and degeneration upon binding proNGF. We have discovered that proNGF, and not mature NGF, is rapidly released into the urine after SCI both in rodents and in humans. Released proNGF in rodents activates p75 in the urothelium, inducing rapid apoptosis of umbrella cells. When we selectively deleted p75 in urothelial cells using conditional knockout strategy with urothelium-specific cre line ($p75^{\Delta}$-UP3a), umbrella cell apoptosis was completely blocked after SCI. We hypothesized that p75 signaling contributes to bladder function under control (spinal intact) conditions and following SCI (complete transection T12-L1). In spinal intact conditions, we evaluated bladder function in conscious $p75^{\Delta}$-UP3a and control $p75^{c}$-UP3a mice. $P75^{\Delta}$-UP3a mice exhibited increased voiding frequency and smaller void volume compared to control. After SCI, however, $p75^{\Delta}$-UP3a mice exhibited increased bladder capacity and intermicturition interval, but overall lower voiding efficiency compared to control. Thus, p75 signaling in the urothelium contributes to micturition

both in control and SCI conditions. ProNGF is released in the CNS after injuries. We evaluated the effect of systemic blocking of proNGF binding to p75 on bladder function using LM11A-31 (100 mg/kg, p.o.; daily) that crosses the blood-brain/spinal cord barrier efficiently and targets p75. Spinal intact mice treated with LM11A-31 exhibited decreased voiding frequency and smaller void volumes similar to that observed in $p75^{\Delta}$-UP3a mice. After SCI, LM11A-31 significantly improved voiding function with overall voiding efficiency reaching that of spinal intact mice. Bladder capacity, intermicturition interval and bladder mass were reduced compared to wildtype mice. LM11A-31 improves motor coordination following SCI without toxicity or exacerbation of pain. These results suggest p75 signaling plays beneficial roles in micturition reflexes in SCI with greater CNS contributions compared to PNS. Blocking p75 action may be a strategy to treat urinary dysfunction after SCI.

**Disclosures: M.A. Vizzard:** None. **K. Tooke:** None. **S. Malley:** None. **N. Ganesh:** None. **F. Farhadi:** None. **J.C. Ryu:** None. **S.O. Yoon:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.14/OO12

**Topic:** F.07. Autonomic Regulation

**Support:** NIDDK R01DK051369

NIDDK R01DK060481

**Title:** Regulation and expression of CXCL chemokines in mouse urinary bladder with inflammation

**Authors: *B. M. GIRARD**, M. GUO, S. MALLEY, M. A. VIZZARD
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**Abstract:** Although the primary insult underlying painful bladder syndrome (PBS)/interstitial cystitis (IC) is not known, it has been suggested that the pathophysiology is a “vicious circle” involving uroepithelial dysfunction, inflammation, afferent nerve hyperexcitability, and visceral hyperalgesia and allodynia. We have hypothesized that pain associated with PBS/IC involves an alteration of visceral sensation/bladder sensory physiology. These changes may be mediated, in part, by inflammatory changes in the urinary bladder. Rodent models suggest potential roles for chemokines in the initiation or maintenance of visceral/pelvic inflammation and pain. Using the cyclophosphamide (CYP)-induced bladder inflammation model, we aimed to characterize further the role of CXCL chemokines (CXCL9, CXCL10 and CXCL11). QRT-PCR and ELISAs were used to determine mRNA and protein expression of CXCL9, CXCL10, and CXCL11 in

urothelium and detrusor. Male and female, wildtype C57BL/6J mice were injected (75 or 150 mg/kg, i.p.) with CYP to induce bladder inflammation (4 hr, 48 hr, chronic). In urothelium of female mice treated with CYP, CXCL10 and CXCL11 mRNA significantly ($p \leq 0.05$) increased with 4 hr and/or 48 hr CYP treatment whereas CXCL10 mRNA increased ($p \leq 0.05$) in the detrusor with 4 hr and chronic CYP treatment and CXCL11 mRNA decreased ($p \leq 0.05$) with 48 hr CYP treatment. In urothelium of male mice treated with CYP, CXCL11 mRNA decreased ($p \leq 0.05$) with 4 hr, 48 hr and chronic CYP treatment. In detrusor of male mice treated with CYP, CXCL9 and CXCL11 mRNA decreased ($p \leq 0.05$) with 4 hr, 48 hr and chronic CYP treatment, whereas CXCL10 mRNA increased ($p \leq 0.05$) with 4 hr and 48 hr CYP treatment. Urinary bladder from control (no CYP) female mice exhibited significantly ($p \leq 0.05$) greater expression of CXCL9 and CXCL10 protein expression compared to bladder from control male mice. In urinary bladder from male mice treated with CYP, CXCL9 and CXCL11 protein expression significantly ($p \leq 0.05$) decreased with chronic CYP treatment and CXCL9, CXCL10 and CXCL11 protein expression was significantly ($p \leq 0.05$) reduced with 48 hr CYP-induced cystitis. CXCL mRNA and protein exhibited differential regulation depending on tissue (urothelium, detrusor), sex and duration of CYP treatment. Ongoing studies are exploring the functional role of these chemokines in micturition reflexes in control conditions and following CYP-induced cystitis. CXCL chemokines may be novel targets for treating urinary bladder dysfunction resulting from urinary bladder inflammation.

**Disclosures: B.M. Girard:** None. **M. Guo:** None. **S. Malley:** None. **M.A. Vizzard:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

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**Program#/Poster#:** 509.15/OO13

**Topic:** F.07. Autonomic Regulation

**Support:** PAPIIT-UNAM IN212916 (MMG)

CONACYT 417840 (RL)

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**Title:** Ventral root avulsion, Effect on micturition and perineal muscles in female rabbit

**Authors: L. ESPINOZA-ALVAREZ**[1], N. RODRÍGUEZ[2], R. LÓPEZ-JUÁREZ[3], R. ZEMPOALTECA[2], F. CSTELÁN[5], X. NAVARRO[6], M. MARTÍNEZ-GÓMEZ[7], *D. L. CORONA QUINTANILLA[4]
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**Abstract:** In mammals the pelvic floor components perform sexual functions and micturition, which are regulated by the brain and spinal cord at the lumbosacral level. The rupture or avulsion of the lumbosacral roots, affects the spinal cord, generating disability and severe sensory, motor and autonomic dysfunctions, such as urinary retention. The studies on ventral root avulsion of the lumbosacral plexus (VRA) show changes in the morpho-functional of the spinal cord and its target organ (lower urinary tract and pelvic and perineal muscles) involved in micturition. In models, as the rat, were showed changes in spinal cord after VRA. However, the distribution of the lumbosacral plexus is different in that model and the anatomofunctional changes in response to the VRA are usually different between species. It is of great importance to determine the changes in micturition and perineal muscles after VRA in the rabbit. Twelve virgin female rabbits (8 months old) divided into two groups. In a group (4) the anatomical arrangement of the lumbosacral plexus and its innervation towards the inferior urogenital apparatus were described. In another group (8) the immediate effect of VRA during micturition was evaluated. Three cycles of micturition were registered through cystrometry, urethral pressure and electromyograms of bulbospongiosus and ischiocavernosus muscles. Subsequently, the ventral roots were avulsionated and after of an hour the micturition were recorded again. The VRA produced immediate shows changes in micturition and in the perineal muscles activity. The VRA in the rabbit affected the micturition, decreasing the bladder and urethral function, which causes dripping during filling and produces hypoactive bladder; together with the inhibition of the electrical activity of the perineal muscles, due to damage in the spinal cord and efferent pathways that regulate the micturition.

**Disclosures: L. Espinoza-Alvarez:** None. **N. Rodríguez:** None. **R. López-Juárez:** None. **R. Zempoalteca:** None. **F. Cstelán:** None. **X. Navarro:** None. **M. Martínez-Gómez:** None. **D.L. Corona Quintanilla:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.16/OO14

**Topic:** F.07. Autonomic Regulation

**Support:** DK093424

**Title:** Propriospinal neurons coordinating activity of external urethral sphincter

**Authors: *S. V. KARNUP**, W. C. DE GROAT
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**Abstract:** Coordination between bladder smooth muscle and striated muscle of the external urethral sphincter (EUS) is of pivotal importance for micturition. In rats efficient voiding depends on the ability of the EUS to produce rhythmic bursts of activity at the peak of bladder pressure. In rats with an intact neuraxis EUS bursting which is mediated by supraspinal circuitry is immediately eliminated after transection of the spinal cord segments rostral to L3/L4 level but recovers along with reflex bladder activity several weeks after transection. However after transection of the cord caudal to L4 bladder reflexes and tonic EUS activity recover, but EUS bursting is lost. This observation has led to the proposal (Chang, H. et.al., AJP Renal, 292, F1044, 2007) that propriospinal connections between reflex circuitry in the L3/L4 spinal cord and motoneurons innervating EUS (EUS-MNs) located in L6/S1 spinal segments are necessary for bladder-sphincter coordination and EUS bursting. To examine the properties of propriospinal and interneurons in the putative L3/L4 bursting circuitry we used whole cell patch clamp techniques in spinal slices to study neurons fluorescently labeled by trans-synaptic viral tracer PRV-GFP (3µl) which was injected into EUS of neonatal male rats between postnatal days 16-18. Neurons were studied 2 days post-infection. During recording neurons were filled with biocytin for mapping and morphological characterization. Cell bodies of fluorescent neurons were located in the dorsal commissure and on both sides of the central canal. Dendrites were distributed within lamina X and medial part of lamina VII. In longitudinal sections rostro-caudal dendrites could be identified at distances as great as 700 µm from the cell body. Electrical stimulation revealed profound excitatory connections within lamina X and VII in transverse slices, and up to 400 µm along the central canal in longitudinal slices. In some cells antidromic spikes were elicited by stimulation of the ventromedial funiculus at distances ranging from 200-350µm from the cell. Local feed-forward inhibition was infrequent and in most cases weak. Injections of depolarizing current steps resulted in tonic firing in the majority of recorded cells and only a small fraction of cells exhibited phasic or single-spike discharges. Thus, intrinsic properties of EUS-related neurons in L3/L4 indicate that they themselves cannot produce rhythmic bursts. Therefore it is likely that they serve as an output of a more complex L3/L4 circuit capable of generating rhythmic burst activity that is transmitted by propriospinal pathways to the EUS-MNs in L6/S1.

**Disclosures: S.V. Karnup:** None. **W.C. de Groat:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.17/OO15

**Topic:** F.07. Autonomic Regulation

**Title:** Increasing bladder capacity in a fully-conscious, large animal model: Sacral nerve stimulation targeted to late stages of bladder fill-cycle has efficacy similar to continuous stimulation

**Authors: *L. ZIRPEL**, T. S. BRINK
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**Abstract:** Introduction Sacral nerve stimulation (SNS; InterStim® Therapy, Medtronic, Inc.) for overactive bladder and fecal incontinence is delivered in a continuous mode. Recent clinical evidence and the emergence of intermittent percutaneous tibial neuromodulation suggest that equal therapeutic efficacy can be achieved with non-continuous SNS. Previous studies in anesthetized rodent demonstrated that SNS during latter parts of the bladder fill cycle elicit an increase in bladder capacity equal to that of continuous SNS. The goal of this study was to use the fully conscious sheep model to test the hypothesis that SNS delivered in the latter part of the bladder fill cycle can elicit the same increase in capacity as continuous SNS. Methods Repeat, single fill cystometry was performed on 8 sheep. Bladder pressure was recorded by a pressure sensor fed through the catheter. Saline (34°C) was infused at 15 ml/min until bladder pressure increased > 30 mm Hg and the sheep assumed voiding posture. The primary measure was bladder capacity = volume of saline infused before voiding. Animals were implanted with bilateral sacral stimulation leads (Medtronic, model 3889) attached to an implanted neurostimulator to deliver SNS (0.21ms pulse width, 10Hz, maximum tolerable amplitude). Maximum tolerable amplitude (MTA) was determined by increasing amplitude until the sheep lifted the ipsilateral leg; amplitude was then decremented until the sheep was weight bearing on the ipsilateral leg. Bladder fill cycle time was determined with three baseline fills. During subsequent fill cycles, stimulation was applied either 1) continuously, 2) during the first half, 3) during the second half, 4) during the last quartile, or 5) during the last decile of the fill cycle. Since the application of SNS was randomized, results were averaged and compared to their respective baselines using a two-tailed *t* test with significance at $p \leq 0.05$. Results Continuous stimulation produced a significant 37% increase in bladder capacity [67±8 ml to 92±6 ml (mean±SD)]. SNS delivered during the first half of the bladder fill cycle did not elicit a significant change in capacity (42±11 ml vs 44±9 ml), whereas SNM delivered during the second half of the bladder fill cycle elicited a significant 74% increase in capacity (46±11 ml to 80±2 ml). SNS during the last quartile of the fill cycle produced a significant 32% increase in capacity (57±9 ml to 75±6 ml), and stimulation during the last decile did not produce a significant change in capacity (55±10 ml to 53±4 ml). Average MTA = 0.79 mA±0.15 (SD). Conclusions These results provide insight into more energy efficient delivery of SNS, as well as to physiologically-triggered therapy.

**Disclosures: L. Zirpel:** A. Employment/Salary (full or part-time):; Medtronic, Inc. **T.S. Brink:** A. Employment/Salary (full or part-time):; Medtronic, Inc..

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** F.07. Autonomic Regulation

**Support:** DK093424

**Title:** Interneurons and propriospinal neurons presynaptic to motoneurons of the external urethral sphincter in rat

**Authors: S. V. KARNUP**, K. KIM, *W. C. DE GROAT
Univ. Pittsburgh Med. Sch., Pittsburgh, PA

**Abstract:** Micturition in rats is dependent on the coordinated activity of parasympathetic and somatic efferent pathways to the bladder and external urethral sphincter (EUS) that originate from the preganglionic neurons (PGN) and motoneurons in L6/S1 segments of the spinal cord. In animals with an intact neuraxis, coordination is mediated by supraspinal circuitry, but after spinal cord injury at the level of the thoracic spinal cord micturition is regulated by spinal reflex circuitry consisting of: (1) a lumbar spinal coordinating center (LSCC) located in the L3/L4 spinal segments and (2) efferent neurons and dorsal commissure interneurons in the L6/S1 cord which receive signals from the LSCC. It is assumed that the LSCC is composed of local interneurons as well as propriospinal neurons (PSN) that project to the L6/S1. To identify the neurons in this putative inter-segmental circuitry in male rats (P30 and P60) we injected pseudorabies virus (3-5 μl) encoding green fluorescent protein (PRV-GFP, courtesy: Dr. L., Enquist) into the EUS and injection of PRV encoding red fluorescent protein (PRV-RFP) into the bladder to trans-synaptically label spinal neurons relevant to lower urinary tract function. Optimal post-infection survival was 3 days for P30 and 4 days for P60. Two populations of neurons presynaptic to EUS-MN were identified: 1) interneurons (INs) in L6/S1 above the central canal (CC) in the dorsal commissure (DCM) and 2) neurons in L3/L4 in the DCM and within 200-300 μm lateral to CC. P30 in comparison to P60 animals exhibited greater numbers of labeled neurons. Neurons presynaptic to bladder PGN were located in similar locations. Small numbers of these neurons were co-labled from bladder and EUS. Injections of a retrograde tracer into the L6/S1 cord co-labeled some PRV labeled neurons in L3/L4 indicating that these neurons belong to a propriospinal (PSN) subpopulation carrying signals from the LSCC to caudal segments. Mapping of labeled cells along the L3/L4 segments revealed clusters of neurons. Grading the intensity of fluorescence among labeled cells allowed for distinguishing brightly stained presumed PSNs from weakly stained local interneurons presynaptic to PSNs. Thus an intraspinal circuit regulating activity of EUS and bladder comprises at least four neuronal subpopulations involved in the control of each organ: (1) efferent neurons in L6/S1, (2) INs in

L6/S1, (3) INs in L3/L4 and (4) PSNs in L3/L4. Co-localization of tracers indicates that some of these neurons are involved in control of both organs.

**Disclosures: S.V. Karnup:** None. **K. Kim:** None. **W.C. de Groat:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant K08 DK101756

NIH Grant P40 RR018604

**Title:** Multiple cortical areas influence the neural regulation of the rat colon

**Authors: *D. J. LEVINTHAL**
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**Abstract:** Descending neural commands from the brain influence the peristaltic, secretory, and immunological functions of the colon. Such commands contribute to colonic changes associated with increased stress or intense emotion, the anticipation of unpleasant events, or changes in physical activity. However, the cortical sources of descending commands to the colon remain poorly understood. To address this issue, we injected rabies virus into the rat distal colon and used the retrograde transneuronal transport of the virus, along with careful adjustment of survival times, to define the cortical areas that influence the colon. Transneuronal transport of rabies virus led to infection of layer V neurons located primarily within three cortical areas: primary motor cortex, secondary motor cortex, and the primary somatosensory cortex. The majority of neurons within these cortical regions were clustered within their respective representations of the trunk and hindlimb. An important component of the descending influences on the colon could be mediated by neural circuits involving an additional synaptic relay. Thus, we extended the survival time to allow one additional stage of transneuronal transport. In these animals, labeled cortical neurons were still found predominantly within three cortical areas: primary motor cortex, secondary motor cortex, and primary somatosensory cortex. However, a notable minority of labeled neurons was also found within the medial prefrontal cortex and the insula. Thus, while sensorimotor regions of the cortex have the most substantial and direct influence on the colon, non-motor cortical regions also gain a less substantial and indirect influence. These findings have important implications for understanding the neural basis for cerebral cortical influences on the colon. First, the presence of labeled neurons within the trunk and hindlimb representations of somatosensory cortical areas provides a direct linkage between the neural control of motor

function and the colon. This neural substrate may explain how physical movement (or lack thereof) influences colonic function and suggests that exercise could be a potential therapy for some colonic disorders. Second, the insula and prefrontal cortex are involved in cognitive and affective processing, and our results imply that these areas are involved in the regulation of colon function. Such connections provide a concrete neural substrate for the influence of cognitive and emotional processes on colonic function. The latter may partly account for the clinical benefits of cognitive behavioral therapy in those with functional gastrointestinal disorders such as irritable bowel syndrome.

**Disclosures: D.J. Levinthal:** F. Consulting Fees (e.g., advisory boards); Associate Editor, Clinical Translational Gastroenterology.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

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**Topic:** F.07. Autonomic Regulation

**Support:** NIH Grant DK106115

NIH Grant DK093424

**Title:** Activation of voltage-gated calcium channels in urinary bladder epithelial cells alters reflex bladder activity

**Authors: *J. M. BECKEL**, S. ALTUNAL, K. A. ROSZKOWSKI, B. Y. TANDOC, C. VENKATRAM, W. C. DE GROAT
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**Abstract:** The release of adenosine triphosphate (ATP) from the epithelial lining of the bladder (urothelium) plays an important role in normal and pathological bladder function. When the bladder stretches during filling, ATP is released from the urothelium and is thought to activate nearby afferent nerves and induce the sensation of bladder fullness. ATP release from the urothelium is increased in patients suffering from overactive bladder, a disorder characterized by an increased desire to void at small bladder volumes. Previous research from our lab indicates that pannexin channels are responsible for urothelial ATP release, although the exact mechanism of channel regulation is unclear. For example, we have demonstrated that urothelial cell membrane depolarization increases ATP release. However this is not thought to be a direct effect of membrane potential on pannexin channels, as the effect was blocked by BAPTA-AM, indicating that intracellular calcium is required. Therefore, our current research examines the possibility that voltage-gated calcium channels exist in the urothelium and that these channels

can modulate urothelial ATP release through pannexin channels. Using RT-PCR and immunofluorescence, we confirmed the presence of several voltage-gated calcium channels in rat ($Ca_V$1.2, 1.4, 2.1, 2.2, 2.3, 3.1, 3.2 and 3.3) and human ($Ca_V$1.3, 2.1, 2.2, 2.3, 3.2 and 3.3) cultured urothelial cells. Moreover, these channels were found to be functional, as stimulation of cultured human urothelial cells with the calcium channel agonist Bay K 8644 (100μM) elicited large intracellular calcium transients, as measured with Fura-2AM. These calcium transients were diminished in the presence of the calcium channel antagonist nifedipine (200μM) and increased in the presence of the calcium-activated potassium channel blocker iberiotoxin (200 nM). Stimulation of cultured human urothelial cells with Bay K 8644 also increased extracellular ATP concentrations by ~25%; and this was blocked by pre-incubation with either nifedipine or the pannexin channel antagonist Brilliant Blue FCF (100μM). Finally, intravesical administration of Bay K 8644 increased reflex bladder activity in the anesthetized rat by almost two-fold, indicating that these channels might play a physiological role in bladder function. These results suggest that urothelial voltage-gated calcium channels participate in the control of micturition and may represent a viable target for the treatment of overactive bladder disorders.

**Disclosures:** **J.M. Beckel:** None. **S. Altunal:** None. **K.A. Roszkowski:** None. **B.Y. Tandoc:** None. **C. Venkatram:** None. **W.C. de Groat:** None.

**Poster**

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**Topic:** F.07. Autonomic Regulation

**Support:** NIH DK106115

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NIH DK054824

**Title:** Modulation of urothelial pannexin channels by intracellular calcium

**Authors: *L. A. BIRDER**[1], A. M. SILBERFELD[2], W. C. DE GROAT[2], J. M. BECKEL[2]
[1]Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [2]Pharmacol. and Chem. Biol., Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** ATP is an important transmitter in the sensory limb of micturition. Release of ATP from the bladder urothelial cells (UTCs) in response to stretch or chemical stimulation can act on nearby afferent nerves to increase their excitability, leading to increased bladder sensations. As patients that suffer from benign bladder pathology such as overactive bladder (OAB) exhibit increased urinary ATP levels, insight into the mechanisms controlling UTC ATP release is an

important step in understanding the etiology of OAB. We have previously determined that ATP release from UTCs in response to stretch is mediated by pannexin channels, large-pore ion channels, permeable to ATP. However, little is known about the intracellular pathways that modulate pannexin channels in UTCs. In other cell types, pannexin channels can be controlled by membrane depolarization, post-translational modifications and intracellular calcium concentrations $[Ca^{2+}]_i$. Given that many studies have already determined that $[Ca^{2+}]_i$ is an important mediator of UTC ATP release, we first focused on this mechanism. Stimulation of a human urothelial cell line (TRT-HU1) with the α3 nAChR agonist cytisine (200μM), which increases $[Ca^{2+}]_i$, increased extracellular ATP concentrations, as measured by the luciferin/luciferase assay. This release was blocked by the pannexin channel antagonist Brilliant Blue FCF (BB-FCF, 100μM). Increasing intracellular calcium using the ionophore ionomycin (1μM) also increased ATP release, which was also blocked with BB-FCF. Pretreatment of cells with the calcium chelator BAPTA-AM (10μM) also blocked increases in ATP release by cytisine or ionomycin. Conversely, treatment of cells with the α7 nAChR agonist choline (5mM) reduced extracellular ATP concentrations, an effect that was mimicked by application of caffeine (1mM), which releases calcium from intracellular stores. To determine if membrane depolarization modulates pannexin channels, cells were stimulated with high potassium (40mM) or the sodium-potassium pump inhibitor ouabain (1mM). Both agents increased extracellular ATP concentrations and were blocked by BB-FCF. ATP release induced by membrane depolarization was also blocked by BAPTA-AM, indicating that depolarization did not have a direct effect on pannexin channels, but most likely activated a voltage-gated calcium channel present in UTCs. These data suggest that intracellular calcium plays a major role in modulating pannexin channel function in UTCs, with influx of extracellular calcium having an excitatory effect and release of calcium from intracellular stores having an inhibitory effect.

**Disclosures: L.A. Birder:** None. **A.M. Silberfeld:** None. **W.C. de Groat:** None. **J.M. Beckel:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

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**Program#/Poster#:** 509.22/OO20

**Topic:** F.07. Autonomic Regulation

**Support:** NIH R01DK099598

**Title:** Liver-related neurons in the paraventricular nucleus of the hypothalamus are more active in db/db mice

**Authors: *A. ZSOMBOK**, H. GAO, A. J. R. MOLINAS, K. MIYATA, X. QIAO
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**Abstract:** Preautonomic neurons in the paraventricular nucleus (PVN) of the hypothalamus contribute to the regulation of hepatic functions via the autonomic nervous system. Despite the importance of the brain-liver pathway, the cellular properties of liver-related neurons remain to be elucidated. Liver-related PVN neurons were identified with a retrograde trans-neuronal viral tracer. Whole-cell patch-clamp recordings were used to test the hypothesis that liver-related PVN neurons are more excited in the diabetic condition. In db/db mice, the majority of liver-related PVN neurons fired spontaneously; whereas, in lean mice the majority of liver-related PVN neurons were silent. Persistent, tonic inhibition was identified in liver-related PVN neurons. The magnitude of tonic inhibitory control was not different between lean and db/db mice. The transient receptor potential vanilloid type 1 (TRPV1)-dependent regulation of liver-related PVN neurons were also investigated. Capsaicin, a potent TRPV1 agonist increased excitatory neurotransmission in lean mice; whereas, capsaicin did not alter neurotransmission of liver-related PVN neurons in db/db mice. These findings demonstrate plasticity of liver-related PVN neurons in a diabetic mouse model and suggest altered autonomic circuits at the level of the PVN; which can contribute to autonomic dysfunction and dysregulation of neural control of hepatic functions including glucose metabolism.

**Disclosures: A. Zsombok:** None. **H. Gao:** None. **A.J.R. Molinas:** None. **K. Miyata:** None. **X. Qiao:** None.

**Poster**

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**Topic:** F.07. Autonomic Regulation

**Support:** NSFC Grant 81202649

**Title:** Effect of electroacupuncture at ST36 and CV12 on visceral sensory in gastric nociceptive stimulus

**Authors: *X. WANG**, W. HE, H. SHI, Y. SU, L. HU, X. JING
Inst. of Acupuncture and Moxibustion, CACMS, Beijing, China

**Abstract: Objectives:** The aim of this study was to observe the effect of electroacupuncture (EA) at ST36 and CV12 on c-fos expression and the firing rate of gastric related neurons in the nucleus of solitary tract (NTS) after intragastric administration of acid. **Methods:** 16 rats were randomly divided into four groups: intragastric physiological saline administration group, intragastric acid administration group, EA ST36 and EA CV12 interference groups. C-fos expression was characterized by morphological observation of immunofluorescence and Westen Blot. And 27 rats were randomly divided into three groups: intragastric acid administration

group, EA ST36 group and EA CV12 group. Neuronal spikes of NTS was recorded by electrode before and after intragastric administration of HCl (0.5 mol/L) . **Results:** Intragastric administration of HCl potently induced expression of c-fos in NTS. Electroacupuncture at ST36 and CV12 inhibited this effect, while EA ST36 showed the more obvious inhibitory effect. Intragastric administration of 0.5M/L HCL led to a rapid increase in integral of firing rates of excitatory neurons in the NTS, which was significant at 90 seconds and remained elevated for 45mins. In the time-window from 8 mins to 30 mins after intragastric acid administration, EA at ST36 and CV12 elicited inhibitory effects on excitatory neurons in NTS, and the inhibition rate of EA ST36 was significantly higher than EA CV12. **Discussion/Conclusion:** In conclusion, EA at ST36 and CV12 regulated gastric nociceptive visceral afferent in NTS in gastric nociceptive stimulus. The difference between the two points possibly suggest the different never afferent. The information of EA at ST36 directly contacted with NTS through the vagus visceral afferent, and information of EA at CV12 contacted with NTS through sympathetic splanchnic afferent with spinal dorsal horn.

**Disclosures:** **X. Wang:** None. **W. He:** None. **H. Shi:** None. **Y. Su:** None. **L. Hu:** None. **X. Jing:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.24/OO22

**Topic:** F.07. Autonomic Regulation

**Support:** FONDECYT #1140776

**Title:** Brain-gut axis: Early-life stress promotes alterations in intestinal permeability and hippocampal 5 HT1A mRNA expression in juvenile rats

**Authors: *J. A. BRAVO**[1], C. ASTUDILLO-GUERRERO[1], J. ESCOBAR-LUNA[1], G. ROSSI-VARGAS[1], C. BARRERA-BUGUEÑO[1], M. GOTTELAND[2], M. JULIO-PIEPER[1]
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**Abstract:** Early-life stress, such as maternal separation (MS) in rodents has been used to model stress-related psychiatric disorders and alterations in intestinal function, however most reports focus on the effects seen at adulthood. Here we evaluated the effect of MS (3h/day from post-natal day (PND) 2 to PND12) on colon barrier function in male Sprague-Dawley rats at PND21 and PND35, and compared them to non-separated (NS) controls. Additionally, through in situ hybridization we evaluated topographical changes in hippocampal 5-HT1A mRNA expression, which is as a marker of stress-related psychiatric disorders. Colon permeability to

macromolecules was evaluated through the everted gut sac technique, applying FITC-conjugated 4.4kDa dextran (FD4.4) on the mucosal side, and then measuring fluorescence in the serosal side for up to 3 hours, while transepithelial electrical resistance (TEER) was determined through Ussing chamber studies. There was no difference in permeability to FD4.4 and TEER between MS and NS at PND21. However, at PND35 there was an increase in permeability to FD4.4 in MS rats when compared to NS, while no differences in TEER where found between both groups. Additionally, when MS rats at PND35 were subjected to a 5min swim stress, they showed a blunted corticosterone response in comparison to swim-stressed NS rats. Furthermore, FD4.4 permeability in swim-stressed MS rats was lower than in non-swim stressed MS rats. In addition, hippocampal 5-HT1A mRNA expression was higher in both layers of the dentate gyrus and cornus ammonis 1 of MS rats in comparison to their controls at PND21.
These data show that early-life stress affects gut permeability to macromolecules at PND35, and that this phenomenon is sensitive to corticosterone. Furthermore, and as opposed as what has been reported in adulthood, early-life stress affects hippocampal 5-HT1A mRNA expression in young animals and is observed as early as PND21, suggesting an alteration in the brain-gut axis that might contribute to the development of stress-related psychiatric disorders later in life.
FUNDED BY: FONDECYT #1140776

**Disclosures:** **J.A. Bravo:** None. **C. Astudillo-Guerrero:** None. **J. Escobar-Luna:** None. **G. Rossi-Vargas:** None. **C. Barrera-Bugueño:** None. **M. Gotteland:** None. **M. Julio-Pieper:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.25/OO23

**Topic:** F.07. Autonomic Regulation

**Support:** NIH R01 NS050514

**Title:** State dependent lower urinary tract reflexes

**Authors: *Z. C. DANZIGER**[1], W. M. GRILL[2]
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**Abstract:** Fluid flow in the urethra can evoked two opposite reflexes that augment continence and micturition. The guarding reflex generates contraction of the external urethral sphincter (EUS) in response to fluid entering the urethra, while the augmenting reflex mediates contraction of the urinary bladder coupled with the relaxation of the EUS in response to fluid entering the urethra. We quantified how sensory feedback from the bladder and urethra interact to determine which of these two functionally opposite reflexes was activated in response to urethral flow. We

quantified urinary tract reflex responses to controlled urethral flow *in vivo* in urethane anesthetized (1.2 g/kg s.c.) female rats (n=12). We isolated and independently filled the bladder and urethra to test a wide range of combinations of bladder volume (from ~30-~160% of the distention evoked reflex threshold volume) and urethral flow rate (0.1-11ml/min) that represent the typical range of physiological stimuli in rat. We found a distinct bladder volume threshold (approximately 75% of bladder capacity) that determined whether the guarding or augmenting reflex was evoked by urethral flow, suggesting a discrete state-dependent transition between continence and micturition-promoting reflexes. Further, we found that the magnitude of EUS contractions during the guarding reflex was proportional to the urethral flow rate, while the magnitude of the bladder contractions during the augmenting reflex was independent of urethral flow rate. Taken together, this evidence indicates that the urinary tract switches between two separate reflex pathways to support micturition and continence by integration of sensory signals from both the bladder and the urethra. This study provides the first quantitative evaluation of how sensory information generated from flow through the urethra and bladder volume interact to engage the micturition reflex or activate the guarding reflex. Characterization of how interacting sensory signals mediate reflexive bladder control is critical for understanding diseases of the lower urinary tract and to guide the development of new treatments.

**Disclosures: Z.C. Danziger:** None. **W.M. Grill:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.26/OO24

**Topic:** F.07. Autonomic Regulation

**Support:** NIH/NIDDK MAPP Research Network Grant U01 DK082370

**Title:** Effects of water avoidance stress on peripheral and central responses during bladder filling in the rat: A multidisciplinary approach to the study of urologic chronic pelvic pain (MAPP) research network study

**Authors: *Z. WANG**[1], H. H. CHANG[2], Y. GAO[2], R. ZHANG[2], Y. GUO[1], L. V. RODRIGUEZ[2], D. P. HOLSCHNEIDER[1]
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**Abstract:** Stress plays a role in exacerbation and possibly development of functional lower urinary tract disorders. Chronic water avoidance stress (WAS) in rats is a model with high construct and face validity to bladder hypersensitive syndromes, such as interstitial cystitis/bladder pain syndrome (IC/BPS), characterized by urinary frequency, bladder hyperalgesia and heightened stress responsiveness. Given the overlap of brain circuits involved

in stress, anxiety, and micturition, we examined the effects chronic stress has on bladder function, as well as its effects on regional brain activation during bladder filling.
Female Wistar-Kyoto rats were exposed to WAS (10 days) or sham paradigms. On day 11, cystometrograms were obtained during titrated bladder dilation, with visceromotor responses (VMR) recorded simultaneously. Cerebral perfusion was assessed during bladder distension (20-cm$H_2O$) following i.v. administration of [$^{14}$C]-iodoantipyrine. Regional cerebral blood flow was quantified by autoradiography and analyzed in 3-D reconstructed brains with statistical parametric mapping.
WAS rats compared to controls showed a decreased pressure threshold and visceromotor threshold triggering the voiding phase. At 20-cm$H_2O$, VMR was significantly greater in WAS animals compared to controls. WAS rats showed greater activation in cortical regions of the central micturition circuit, including the posterior cingulate, anterior retrosplenial, somatosensory, posterior insula, orbital, and anterior secondary (supplementary) motor cortices, as well as in thalamus, hypothalamus, striatum, parabrachial and Barrington nuclei. Seed analysis showed increased functional connectivity of WAS compared to control rats of the posterior cingulate cortex to the pontine parabrachial nucleus; of the Barrington nucleus to anterior dorsal midline and ventrobasilar thalamus and somatosensory and retrosplenial cortices; and of the posterior insula to anterior secondary motor cortex.
Our results show a visceral hypersensitivity during bladder filing in WAS rats, as well as increased engagement of portions of the micturition circuit responsive to urgency, viscerosensory perception and its relay to motor regions coordinating imminent bladder contraction. Results are consistent with findings in humans with IC/BPS, suggesting that WAS may serve as an animal model to elucidate the mechanisms leading to viscerosensitive brain phenotypes in patients. Ongoing work is evaluating the effects of ceftriaxone, a modulator of the glutamate transporter previously reported to diminish hyperalgesia in the WAS model, on functional brain responses of the micturition circuit.

**Disclosures: Z. Wang:** None. **H.H. Chang:** None. **Y. Gao:** None. **R. Zhang:** None. **Y. Guo:** None. **L.V. Rodriguez:** None. **D.P. Holschneider:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.27/OO25

**Topic:** F.07. Autonomic Regulation

**Title:** Hypothalamic PVN neurons rapidly modify circulating insulin levels

**Authors: *I. PAPAZOGLOU**, Z. CUI, J.-H. LEE, S. G. RANE
NIDDK, Bethesda, MD

**Abstract:** Insulin is secreted from pancreatic ß-cells in response to changes in levels of circulating nutrients and hormones. This process is tightly regulated by the autonomic nervous system that strongly innervates the pancreatic islets. Although the role of intra-islet effects of autonomic nerve terminals is well studied, little is known about the way preautonomic centers in the central nervous system regulate insulin secretion. Retrograde tracing studies using PRV (pseudorabies virus) have shown that the highest density of second order preautonomic neurons for both sympathetic and parasympathetic innervation of pancreas are located within the paraventricular nucleus (PVN) of the hypothalamus. We are using chemogenetics to manipulate the activity of specific neuronal populations in the PVN and monitor changes in circulating insulin levels. We stereotactically inject AAV viruses that induce the expression of DREADDs (Designer Receptor Exclusively Activated by Designer Drugs) in the PVN. These receptors (excitatory or inhibitory) can only be pharmacologically activated by a synthetic ligand injected intraperitoneally. We find that stimulation of Sim1 neurons in the PVN results in a rapid decrease in glucose stimulated insulin secretion (GSIS) which is accompanied by an increase in glucose levels. Notably, stimulation of these neurons also significantly suppresses basal fasting insulin levels. Chemogenetic inhibition of Sim1 neurons, on the other hand, significantly enhances GSIS and reduces glycemia. Further, stimulation of a smaller population of PVN neurons, the oxytocin (OXT) neurons, leads to a rapid improvement of GSIS. To characterize this neuronal network, we are testing the role of autonomic preganglionic neurons downstream of the PVN. To achieve this, we use an AAV-Cre virus than can travel anterogradely from the PVN to the brainstem (parasympathetic neurons) or the spinal cord (sympathetic neurons). A second AAV virus injected locally will induce Cre-dependent expression of DREADDs, so that only neurons that receive projections from the PVN express these receptors. Finally, it is important to know if Sim1 neurons can sense acute changes in blood glucose. To assess that, we are using *in vivo* photometry to monitor the activity of Sim1 neurons in hyper- or hypoglycemic states. Taken together, the findings of this study will lead to a functional characterization of neurocircuits that are implicated in the central regulation of insulin secretion.

**Disclosures: I. Papazoglou:** None. **Z. Cui:** None. **J. Lee:** None. **S.G. Rane:** None.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.28/OO26

**Topic:** F.07. Autonomic Regulation

**Support:** Medtronic Inc.

**Title:** Comparison of bladder inhibitory effects of patterned spinal nerve stimulation with conventional neuromodulation in the rat

**Authors: *X. SU**, H. A. SIMENSON, K. J. PARALIKAR, H. D. ORSER
Medtronic, Minneapolis, MN

**Abstract:** Electrical stimulation of the sacral spinal nerve has been used in the treatment of patients with increased frequency and urge incontinence. The frequency of continuous, fixed 10 Hz stimulation is optimal in both measures of isovolumetric of “normal” bladder (1) and cystometry of hypersensitive bladder of cystitis (2). The present study compared the effectiveness of patterned frequency of spinal nerve stimulation (SNS) with continuous, fixed-frequency nerve stimulation at motor threshold intensity in an animal model of the bladder reflex contraction (BRC). In anesthetized female rats (urethane, i.p. 1.2g/kg), wire electrodes were placed under each of the L6 spinal nerve to produce bilateral SNS. A cannula was placed into the bladder via the urethra and the urethra was ligated to ensure an isovolumetric bladder. Saline infusion induced BRC. Using motor threshold intensity, continuous stimulation at fixed frequencies of 4 Hz (n=5) and 10 Hz (n=7) decreased the frequency of BRC of 71 ± 24% (mean, SEM) and 85 ± 18% of controls, respectively (v.s. no stimulation, n=10, $p<0.05$, two-way ANOVA). Fixed-frequency stimulation at 0.01, 0.1, 1, 40, and 100 Hz did not demonstrate a trend change on BRC. When stimulation frequency is delivered with a 4-6 pulse/burst pattern in every 1-100 seconds, neuromodulation has demonstrated a trend towards effectiveness, with a four-pulse burst stimulation (interburst 1 Hz and intraburst 40 Hz or 4 pulses of 40 Hz per second) showing the most difference, reducing the BRC frequency of 74 ± 8% of control, n=8, $p<0.05$, two-way ANOVA). However, it is not more effective than continuous neuromodulation at a fixed frequency of 4 Hz or 10 Hz at BRC inhibition. Secondary to efficacy, saving energy is an important factor to increasing a device's lifespan. We report that burst stimulation is not more effective than continuous neuromodulation and does not offer an energy saving benefit. Without further knowledge regarding mechanisms and potential benefit of burst stimulation on bladder control in patients with neuropathological conditions, applications should utilize continuous fixed 10 Hz stimulation for maximal clinical outcomes.
References:

1. Su X, Nickles A, Nelson DE. Neuromodulation in a rat model of bladder micturition reflex. Am J Physiol Renal Physiol 2012; 302: F477-F486.

2. Su X, Nickles A, Nelson DE. Optimization of neuromodulation for bladder control in a rat cystitis model. Neuromodulation 2016; 19:101-107.

**Disclosures: X. Su:** A. Employment/Salary (full or part-time):; Medtronic Inc. **H.A. Simenson:** A. Employment/Salary (full or part-time):; Medtronic Inc. **K.J. Paralikar:** A. Employment/Salary (full or part-time):; Medtronic Inc. **H.D. Orser:** A. Employment/Salary (full or part-time):; Medtronic Inc.

**Poster**

**509. Gastrointestinal, Renal, Urinary, and Reproductive Regulation II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 509.29/OO27

**Topic:** F.07. Autonomic Regulation

**Support:** PAPIIT-UNAM IN212916 (MMG)

CONACYT 417840 (RL)

CONACYT 256990 (CQDL)

**Title:** Effect on pelvic floor muscles activity, simulating changes during multiparity

**Authors: *R. LOPEZ JUAREZ**[1], R. ZEMPOALTECA[1], D. CORONA[1], F. CASTELAN[1,2], M. MARTINEZ-GOMEZ[2]
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**Abstract:** In women, pelvic floor dysfunctions are a major public health issue because their high prevalence and negative impact on quality of life. One of the main functions were affected is the urinary. We reported that blocking the activity of perineal muscle bulbospongiosus (Bsm), ischiocavernosus (Iscm) and pelvic muscle as the pubococcygeus (Pcm) causes changes in micturition. In multiparous young rabbits we have shown that the histological arrangement of the genitourinary apparatus is modified. Other changes include urodynamic function, contractile force and morphometry of the pelvic floor muscles and paravaginal pelvic plexus. Possibly, during passage of the fetus by vagina the nerves would suffer damage and cause urinary and sexually dysfunctions. Virgin and multiparous female chinchilla rabbits (10 to 12 months old) were used in the study. Cystometrograms were recorded simultaneously with electromyograms, before and after crushing of Bsm or Pcm nerves were evaluated. After the crushing of the Bsm nerve, the urodynamic parameters showed a decrease in voiding volume, maximum pressure and bladder efficiency ($P<0.001$) and increase in residual volume. When the Pcm nerve was crushing, the voiding volume, interval between contractions, threshold pressure, maximum pressure and bladder efficiency decreased ($P<0.001$) and the residual volume increased ($P<0.001$). In multiparas, voiding volume, interval between contractions, threshold pressure, maximum pressure and bladder efficiency decreased ($P<0.001$) and the threshold volume and residual volume increased ($P<0.001$). Electromyographic records show Bsm activity during the voiding phase and the Pcm during urine storage. The activity of the Pcm and Bsm after crushing the electrical activity were decreased and disorganized. Crushing modify the bladder function by

reducing bladder efficiency due to the increase in residual volume. Crushing to the nerve of the Bsm or Pcm seems to simulate some of the alterations produced in the multiparity model.

**Disclosures: R. Lopez Juarez:** None. **R. Zempoalteca:** None. **D. Corona:** None. **F. Castelan:** None. **M. Martinez-Gomez:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.01/OO28

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIH Grant DK-52849

**Title:** NPY/PYY receptor activation in the dorsal vagal complex increases food intake and attenuates satiation

**Authors: *R. C. RITTER**, N. HUSTON, L. BRENNER
Dept. of Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA

**Abstract:** Although fourth ventricle or parabrachial injections of NPY/PYY receptor agonists are reported to increase food intake, it is not known whether selective activation of NPY/PYY receptors in the dorsal vagal complex (DVC) contributes to control of food intake. To investigate this possibility, we first used fluorescence in situ hybridization to survey the prevalence of NPY/PYY receptor subtypes, Y1R, Y2R and Y5R, in vagal afferent neurons, and in the DVC, including the nucleus tractus solitarius (NTS). Many vagal afferent neurons in the nodose ganglia expressed Y1R and/or Y2R mRNA. Y2R mRNA often was co-expressed with mRNA coding for CCK-A receptor. Y1R, Y2R and Y5R expressing neurons were rare or not detectable in the NTS. These observations confirm the presence of Y1R and Y2R in the DVC, where previous immunohistochemical observations suggested their expression on vagal afferent endings, and also on some NTS neurons. To determine the effects of DVC Y2R activation on food intake and satiation, we implanted rats with cannulas aimed for the left or right DVC, and measured 4h food intake following NTS injection of a selective Y2R agonist, PYY 3-36 (100 ng/100nl), during the morning, beginning 2h after lights-on. In another group of rats we examined the effect of NTS PYY 3-36 (200 ng) injection on reduction of food intake following intraperitoneal (IP) injection of CCK (3 μg/kg) in rats following an overnight 15hr fast. To verify cannula placements and patency, we injected 100 nl biotintylated dextran (BDA) via the DVC cannulas, just before collecting brains for histology. Incubation of brain sections with Alexa 488 IB4 and Alexa 555 avidin revealed NTS vagal afferent terminals and the spread of BDA injections respectively. Only rats with cannula tips located in the DVC, and BDA infiltrating the NTS, as delineated by IB4 labeling, were accepted as valid placements. We found that DVC injection of PYY 3-36

(100 ng) significantly increased food intake over 4h in sated rats with verified NTS placements (N= 9). Rats with placements in which BDA injection did not infiltrate the NTS did not significantly increase their intake. Co-injection of Y2R antagonist into the NTS together with PYY 3-36, attenuated increased food intake (N=6). Finally, NTS injection of PYY 3-36 significantly attenuated or abolished reduction of food intake by IP CCK (N=10). These results indicate that selective activation of YR within the DVC increases food intake and attenuates CCK-induced satiation. Furthermore, our results are consistent with the hypothesis that Y2R located on central vagal afferent endings mediate increased food intake and reduced satiation following hindbrain PYY 3-36 injections.

**Disclosures: R.C. Ritter:** None. **N. Huston:** None. **L. Brenner:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.02/OO29

**Topic:** F.10. Food Intake and Energy Balance

**Support:** FOSSIS 233918

**Title:** Anorexigenic effect of alpha-melanocyte stimulating hormone in nucleus accumbens is mediated by frontal cortex throtropin-releasing hormone and dopamine pathways in rats

**Authors: *E. ALVAREZ**[1], F. GAMA[2,3], P. DE GORTARI[2]
[1]Neurociencias, Inst. Nacional De Psiquiatria, Mexico City, Mexico; [2]Inst. Nacional de Psiquiatria, Mexico City, Mexico; [3]Escuela de Dietetica y Nutricion del ISSSTE, Mexico City, Mexico

**Abstract:** A wide array of neuropeptides and peripheral molecules act in the central nervous system to control food intake. Apart from the homeostatic aspects of food intake, hedonic regulation is crucial in modern societies where palatable food is readily available. Hypothalamus is considered as the regulator of the homeostatic aspect of feeding, while the mesolimbic system (containing the nucleus accumbens [NAcc]) is involved in the control of the hedonic aspects of this behavior via dopamine (DA)ergic signaling. Neuropeptides from the hypothalamic arcuate nucleus, including α-melanocyte stimulating hormone (α-MSH), are some of the most potent modulators of food intake. α-MSH acting in the paraventricular hypothalamic nucleus (PVN) enhances the expression of another anorexigenic neuropeptide, thyrotropin releasing hormone (TRH). α-MSH administration into the NAcc reduces food intake motivation and induces DA release. NAcc has projections to the prefrontal cortex (PFC) a region which by DA signaling is related to decision-making and food seeking behavior. PFC expresses high densities of DA containing terminals, and DA activity in this region is enhanced during feeding after food

deprivation. Since α-MSH directly modulates TRH expression in the PVN and TRH is also expressed in the Nacc, we were interested in analyzing if α-MSH actions when injected intra-NAcc, are mediated through TRHergic neurotransmission and the role of the PFC DAergic signaling as the possible ultimate target. Male rats were fasted for 48h and injected with α-MSH directly into the Nacc before refeeding. Animals showed a significant decrease in food intake after refeeding and an enhanced expression of TRH in the Nacc. Moreover, DA receptor 2 (D2R) expression was increased in the PFC after α-MSH injection in the NAcc. PFC administration of an antisense oligo directed against TRH-receptor type 2 (TRH-R2), but not to the receptor type 1, was able to reverse both the decrease in food intake and the increase in D2R expression in the PFC induced by α-MSH. In conclusion, α-MSH administration into the NAcc activated TRHergic neurons in this nucleus, which by their afferents to the PFC, and by acting through its TRH-R2 receptors; mediated the anorexigenic effects of α-MSH. Moreover, it is possible that changes in DA signaling in the PFC are also involved in this effects of α-MSH mediated by TRH. This implicates TRH not only as a modulator of energy homeostasis but in regulation of hedonic feeding.

**Disclosures:** **E. Alvarez:** None. **F. Gama:** None. **P. de Gortari:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.03/OO30

**Topic:** F.10. Food Intake and Energy Balance

**Title:** Neuropeptide Y modulates discrete elements of prey capture via receptors in the optic tectum

**Authors: *J. A. CARR**[1], R. ISLAM[1], B. N. HARRIS[2]
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**Abstract:** The optic tectum (in non-mammalian vertebrates) and superior colliculus (in mammals) rapidly inhibit food intake when a visual threat is present. Previous anatomical and electrophysiologial evidence in toads (Bufo sp.) suggest that neuropeptide Y (NPY), originating from cells in the thalamus, may play a role in the inhibition of tectally mediated prey capture. Here, we ask the question, do tectal NPY receptors modulate food intake in juvenile *Xenopus laevis*? Specifically, we asked 1) does the anuran tectum possess Y2 receptors? 2) does tectal NPY administration alter prey-capture behavior? 3) does tectal NPY administration decrease food intake? Using immunohistochemical and immunoblotting approaches we found that the tectum of *X. laevis* is richly innervated with Y2 receptor-immunoreactive axons and terminal fields. To determine whether NPY acts on tectal receptors to alter prey capture behavior and food intake, we administered various doses of porcine NPY (0, 1.5, 15, 150 ng) bilaterally into the

tecta of juvenile frogs. Frogs were then subjected to a prey capture behavioral assay and behavior was video recorded and analyzed using JWatcher. NPY injected via the tecta failed to significantly reduce food intake at any dose tested. However, NPY differentially altered discrete components of prey capture behavior. The largest dose of NPY (150 ng) increased the latency to contact food, and reduced the amount of time in contact with food and the number of mouth wipes. NPY did not significantly alter arm sweeps or time spent exploring or moving. We conclude that NPY acts in a dose dependent fashion on receptors in the tectum to slow the approach toward potential prey and accelerate food consumption when food is contacted. Whether these behaviors facilitate predator avoidance while feeding will require further testing. This work was done in partial completion of requirements for the Master's degree at Texas Tech University (R.I.)

**Disclosures: J.A. Carr:** None. **R. Islam:** None. **B.N. Harris:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.04/OO31

**Topic:** F.10. Food Intake and Energy Balance

**Support:** Carver Trust

**Title:** Requirement of MRAP2 for ghrelin-mediated hunger sensing

**Authors: *T. YIN**[1], D. SRISAI[3], A. LEE[1], A. ROUAULT[1], J. A. SEBAG[2]
[2]Mol. Physiol. and Biophysics, [1]Univ. of Iowa, Iowa City, IA; [3]molecular physiology and biophysics, Univ. of Iowa / F.O.E.D.R.C., Iowa City, IA

**Abstract:** Ghrelin is the only known circulating orexigenic hormone. It is primarily secreted by the stomach and acts at its receptor, GHSR1a, in the hypothalamus to signal hunger and promote food intake. For this reasons, the modulation of ghrelin signaling is a promising strategy for the treatment of obesity, anorexia, cachexia and diabetic gastroparesis. In this study we identify the melanocortin receptor accessory protein 2 (MRAP2) as a critical new partner of GHSR1a. We show that MRAP2 interacts with GHSR1a and strongly potentiates ghrelin-stimulated signaling both *in-vitro* and *in-vivo*. Additionally, we show that the orexigenic effect of ghrelin is lost in *Mrap2* KO mice. Finally, we demonstrate that, in the absence of MRAP2, fasting fails to activate AGRP neurons. Our results suggest that MRAP2 is an important modulator of the energy homeostasis machinery that operates through the regulation of multiple GPCRs throughout the hypothalamus.

**Disclosures:** **T. Yin:** None. **D. Srisai:** None. **A. Lee:** None. **A. Rouault:** None. **J.A. Sebag:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.05/OO32

**Topic:** F.10. Food Intake and Energy Balance

**Title:** The effect of methadone in the consumption of a high carbohydrate diet at weaning and its repercussion on the intake of hypercaloric diet in adult male rats

**Authors: *J. A. MATA-LUÉVANOS**[1], J. JUAREZ[2]
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**Abstract:** Overweight and obesity have become a health issue, which, in most cases is due to high intake of palatable food. This palatability is mostly based on the caloric density, making hypercaloric food the most preferred. High consumption of hypercaloric food, often high in carbohydrates (carbs), may produce aberrant patterns of eating, among other problems. There is evidence that infancy may be a critical period for the exposure to food with high content of carbs and fat, which in turn may have an important impact on the choice of food and eating patterns on later life. Maturation of some neurotransmission systems at this age and the implication of opioids in the hedonic salience of stimuli, suggest that alterations of this pathway may play an important role in the salience of alimentary stimuli. On this basis, the effects of methadone (opioide agonist) administration (MA) on the consumption of high-carbs food during pre-adolescence and its repercussion on the consumption of a hypercaloric food in adulthood were studied. Four groups of male Wistar rats were exposed to different pharmacologic treatment on infancy during 18 days, starting at 23 postnatal day (PND), which was associated to the exposure to a food rich in carbs (CHO); at 75 PND, as adults, all groups received a hypercaloric diet (HCD, rich in carbs and fat) during 4 weeks. Food intake and body weight were registered. Groups: METCHO: MA prior CHO presentation. CHOMET: MA after CHO presentation. VEHCHO: Vehicle Administration (VA) prior CHO presentation. CHOVEH: VA after CHO presentation. Base line (BL) of only standard food was measured at 70-75 PND; post-treatment (PT) assessment with only standard food at 103-108, and all animals were re-exposed (RE) to the HCD at 108-113. Group CHOMET showed the highest consumption of CHO diet in preadolescence; however, there were not group differences in the body weight. Higher consumption of HCD diet was observed in CHOMET during adulthood, but interaction (groups X weeks) indicated that differences were significant respect of METCHO and VEHCHO in week 2. After the four weeks under HCD exposure, all groups showed a decrease in standard food

consumption in PT period, which was significantly lower than intake in BL. In the period of HCD exposure, CHOMET gained more weight than VEHCHO and METCHO in week 2 and only than VEHCHO in week 1. Body weight gain was significantly lower in PT than in BL regardless of group. Results support that opioid system plays an important role in the consummatory phase of the alimentary behavior, and that preadolescence is a critical period for feeding behavior.

**Disclosures: J.A. Mata-Luévanos:** None. **J. Juarez:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.06/OO33

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIDDK grant DK092322

BBRF NARSAD Young Investigator Award to PRB

**Title:** Tryptophan related genes in the gut microbiome are associated with hunger and are modified by long term resistant starch supplementation

**Authors: *A. NEFF**[1], K. A. NOWAK[2], K. E. CHAPPELLE[2], P. R. BURGHARDT[2]
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**Abstract:** The average western diet is too high in calories, leading to obesity, type II diabetes, and other health complications. Behavioral and neurobiological interventions have had some success at reducing food intake, but often have side effects or lack efficacy. One supported approach is modulating plasma tryptophan (trp) levels, which is related to brain serotonin. Many factors influence trp regulation, most importantly diet and exercise, but growing evidence supports a role for the gut microbiome in influencing host metabolism, and even contributing to amino acid homeostasis. Our research seeks to understand whether a prebiotic supplement of resistant starch (RS), which has a demonstrated ability to affect gut bacteria, can alter gut bacterial trp production and ultimately diet.
Healthy men and women were recruited for these studies. Prior to the first visit, subjects provided a fecal sample, 4-day diet log, and were given an acute dose of RS. Hunger and craving were assessed using a visual analog scale. The initial visit was followed by a four week daily RS supplementation and a second visit. We evaluated mRNA expression for one trp producing gene (TrpB of the trp operon) and one trp degrading gene (TnaA, tryptophanase), in a highly abundant species in the human gut, *Bacteroides ovatus*. With a limited sample size (n=5), we observed an inverse relationship between the pre/post supplement changes in TrpB and TnaA. The inverse

relationship between TrpB and TnaA expression supports the hypothesis that these genes are subject to similar regulatory forces influenced by dietary patterns. Following 4-weeks of RS-supplementation, hunger was correlated with decreased TrpB and increased TnaA expression. This is consistent with the hypothesis that aspects of food intake can be influenced by alterations in gut-microbe mediated trp availability to the host. This work begins to address the potential role of the gut microbiome on neurotransmitter substrate availability and host behavior.

**Disclosures:** **A. Neff:** None. **K.A. Nowak:** None. **K.E. Chappelle:** None. **P.R. Burghardt:** None.

**Poster**

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**Topic:** F.10. Food Intake and Energy Balance

**Support:** NSF IOS-1121886 (MBP)

MH104384 (RTL)

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**Title:** Post-meal optogenetic inhibition of dorsal or ventral hippocampal glutamatergic neurons promotes meal initiation and increases energy intake

**Authors: *R. C. HANNAPEL**[1], J. RAMESH[1], R. T. LALUMIERE[2], M. B. PARENT[1]
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**Abstract:** The majority of research investigating the neural control of food intake has focused on homeostatic and hedonic mechanisms, with relatively few studies examining the contributions of brain regions traditionally associated with cognition. Increasing evidence, including our own, strongly indicates that dorsal (dHC) and ventral (vHC) hippocampal neurons, which are critical for memory, also regulate ingestive behavior. Memory can be a powerful mechanism for influencing eating behavior because it provides a record of recent energy intake that can outlast most physiological signals. We demonstrated previously that muscimol-induced inactivation of dHC or vHC neurons after the end of a sucrose meal, when the memory of the meal would be consolidated, accelerates the onset of the next meal and increases intake during the following meal. Centrally infused muscimol, however, inhibits neural activity for several hours and can affect all cells expressing GABAA receptors. If dHC and vHC neurons control intake through a process that involves memory, then optogenetic inhibition of principal dHC or vHC

glutamatergic neurons restricted to the period immediately following a meal should promote meal initiation and increase intake. In the present experiment, male Sprague-Dawley rats were stereotactically injected with AAV-CaMKIIα-eArchT3.0-eYFP or a control vector (AAV-CaMKIIα-GFP) into dHC or vHC and a fiber optic probe was implanted above the AAV infusion site. Our results indicate that optical inhibition of dHC or vHC glutamatergic neurons for 10 min after a sucrose or chow meal decreases the latency to eat again and increases intake during the next meal when the neurons are no longer inhibited. These results support the hypothesis that dHC and vHC glutamatergic neurons, which are essential for memory, are also critical for regulating energy intake during the postprandial period.

**Disclosures: R.C. Hannapel:** None. **J. Ramesh:** None. **R.T. LaLumiere:** None. **M.B. Parent:** None.

**Poster**

**510. Control of Feeding and Satiety**

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**Program#/Poster#:** 510.08/OO35

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NARSAD Young Investigator

PNI Innovation Award

Shapiro-Silverberg Fund

**Title:** Identification of a brainstem circuit controlling energy balance

**Authors: *A. R. NECTOW**[1], M. SCHNEEBERGER[2], H. ZHANG[4], B. FIELD[5], N. RENIER[3], M.-H. HAN[6], J. FRIEDMAN[7]
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**Abstract:** Hunger, driven by negative energy balance, elicits the search for and consumption of food. These effects are elicited through changes in the natural activity patterns of neurons in the hypothalamus and elsewhere. We have recently identified two populations of neurons within the brainstem's dorsal raphe nucleus (DRN), expressing vesicular transporters for either GABA or glutamate (hereafter, DRN Vgat or DRN VGLUT3 neurons, respectively), that are responsive to physiologic stimuli encoding hunger- and satiety-related states. Furthermore, these two populations can potently and reciprocally regulate food intake and related behaviors, over both acute and prolonged timescales. Local and global connectivity mapping suggests multiple

mechanisms through which these neurons may alter feeding and related behaviors. This work demonstrates the cell type-specific mechanism through which the DRN regulates feeding.

**Disclosures:** **A.R. Nectow:** None. **M. Schneeberger:** None. **H. Zhang:** None. **B. Field:** None. **N. Renier:** None. **M. Han:** None. **J. Friedman:** None.

**Poster**

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**Program#/Poster#:** 510.09/OO36

**Topic:** F.10. Food Intake and Energy Balance

**Support:** HFSP Long-term Fellowship

JPB Foundation

HHMI

**Title:** Driving satiety through the control of hippocampal hilar mossy cells

**Authors: *E. AZEVEDO**[1], M. SCHNEEBERGER[1], S. STERN[1], J. CHENG[2], L. POMERANZ[1], P. GREENGARD[2], J. FRIEDMAN[1]
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**Abstract:** Obesity is a serious illness affecting more than one-third of the adult population, and alarmingly, more than 17% of children in the USA. Obesity is associated with high mortality and increased risk of developing other medical conditions, such as diabetes. To fight obesity, the gain of knowledge on how neural circuits control feeding is vital. There are about two decades of evidence suggesting that the hippocampus, an important brain region associated with episodic memory, may control feeding. However, the mechanism by which hippocampal neurons modulate feeding and its underlying circuit remains unclear. We reasoned that the hippocampus must respond to food in a similar manner as time cells and place cells are activated by temporal or spatial changes respectively. We believe that visual, gustatory or odorant appetitive cues may be able to activate specific hippocampal cells in order to create a food engram and thus, communicate with existing feeding circuits. Thus, the molecular identification of a specific ensemble that fires in response to food or eating would enable us to perform a functional analysis of the high-order circuit that modulates energy intake by the hippocampus. Here, we report the unbiased description of a molecularly defined neuronal population within the hippocampus that expresses dopamine 2 receptor (D2R) and that is activated by appetitive cues and energy states. The selective inhibition or activation of D2R neurons using chemogenetics is sufficient to induce changes in food intake. Moreover, projection-specific manipulations of these neuronal connections using optogenetics reveal a novel extrahippocampal circuitry that project to the

septal and cholinergic basal forebrain and control feeding behavior. These findings describe a previously unidentified role for hilar mossy cells within the hippocampus and shed light on how food cues can suppress feeding through activating a specific hilar mossy cells to septal cells circuitry.

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**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

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**Program#/Poster#:** 510.10/PP1

**Topic:** F.10. Food Intake and Energy Balance

**Title:** Elucidating metabolic and molecular mechanisms by which intermittent fasting enhances endurance and brain function in mice

**Authors: *K. MOEHL**, K. MAROSI, M. P. MATTSON
Natl. Inst. On Aging, Baltimore, MD

**Abstract:** Evolutionary considerations suggest that the brain and body have been optimized to perform well/optimally in the fasted state (*Ageing Res Rev.* 2015; 20:37-45). Sports physiologists and endurance athletes are currently investigating nutritional ketosis as a potential method for attenuating the decrease in physiological performance associated with the decline in endogenous carbohydrate stores. The increase in lipid oxidation associated with the metabolic switch to a ketogenic state has been shown to have beneficial effects on the brain as well as muscles. Because fasting is the most potent physiological stimulus for ketosis, we designed a study to determine the impact of intermittent fasting during endurance training on performance, and to elucidate the underlying cellular and molecular mechanisms. C57BL/6 male mice were randomly assigned to either *ad libitum* feeding or alternate day fasting (ADF) groups, and half of the mice in each diet group were trained daily on a treadmill for 1 month (45 minutes of running with increasing speed or incline each week). A run to exhaustion endurance test performed at the end of the training period revealed superior performance in the mice maintained on ADF during training compared to mice fed *ad libitum* during training. Mice in the ADF-running group displayed a lower respiratory exchange ratio throughout the $VO_2$ max test, improved glucose homeostasis, and elevated ketone levels. These findings, supported by the literature, suggest that the increased contribution of lipid and ketone bodies oxidation to energy provision during exercise may be beneficial for endurance running performance. The potential benefits of exercise in a ketogenic state on a range of brain functions (cognition, anxiety, motor skills) are currently being investigated. Analyses of gene expression in cerebral cortex, hippocampus, liver, and soleus tissues, and metabolomics analysis of blood suggest that the metabolic switch invoked by

intermittent fasting and exercise modulates a wide range of molecular pathways including those regulating mitochondrial biogenesis, autophagy and cellular plasticity. Supported by the NIA Intramural Research Program.

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**Poster**

**510. Control of Feeding and Satiety**

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**Topic:** F.10. Food Intake and Energy Balance

**Support:** DA038168 (GDS)

DA032750 (GDS)

DK112564 (MAR)

T32NS007431 (MLB)

**Title:** Transcriptional profiling of lateral hypothalamic cell types following obesity at cellular resolution

**Authors: *M. L. BASIRI**[1], M. A. ROSSI[1], G. D. STUBER[2]
[2]Psychiatry, [1]Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

**Abstract:** The lateral hypothalamic area (LHA) mediates a broad range of motivated behaviors. In particular, historical and contemporary work has described the LHA as an essential substrate in the regulation of feeding behavior and caloric intake. To mediate its diverse functional tasks, the LHA exhibits broad molecular heterogeneity, with intermingled LHA cell types employing distinct neurotransmitter and neuropeptide systems. Although recent work has broadly described the functional involvement of inhibitory and excitatory LHA circuits in feeding behavior, the specific cell types underlying discrete LHA behavioral functions remains relatively unknown, and whether LHA molecular representations are sculpted by chronic caloric excess has not been explored. Here, we perform massively-parallel single-cell RNA sequencing across 20,194 LHA cells to characterize LHA transcriptional diversity following ad libitum access to a high-fat diet versus a taste-matched control. By comparing transcriptional profiles across cells, we identify discrete LHA neuronal and glial cell types, and identify novel potential markers for distinct LHA neurocircuit activities. Furthermore, we describe global diet-induced LHA molecular reprogramming and identify putative molecular pathways underlying behavioral changes during obesity. This work provides a molecular foundation to explore how transcriptional definitions

may inform circuit dynamics and behavioral output in complex neuronal tissue, as well as how these definitions may be altered in response to divergent systemic conditions.

**Disclosures:** **M.L. Basiri:** None. **M.A. Rossi:** None. **G.D. Stuber:** None.

**Poster**

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**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIDA Grant DA038168

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NIDA Grant DA041184

**Title:** Activity of glutamatergic neurons in lateral hypothalamus is suppressed by obesity

**Authors: *M. A. ROSSI**, M. L. BASIRI, J. M. OTIS, H. VAN DEN MUNKHOF, J. A. MCHENRY, O. KOSYK, W. GUO, G. D. STUBER
Univ. of North Carolina-Chapel Hill, Chapel Hill, NC

**Abstract:** The lateral hypothalamic area (LHA) is a molecularly and functionally heterogeneous region that is critical for motivated behaviors. Glutamatergic neurons within the LHA are known to influence feeding and reward phenotypes; acute activation of LHA glutamatergic neurons suppresses feeding, while ablation facilitates intake of calorically dense foods and weight gain. Given the established role of these neurons in feeding, we sought to determine whether the activity profiles of LHA glutamatergic neurons reflect satiety state and how this activity changes during the onset of obesity. Using *in vivo* deep brain two-photon calcium imaging in awake, behaving mice, we found that LHA glutamatergic neurons exhibit relative suppression of activity during consumption of a sucrose solution when mice are fasted compared to when they are fed. We then induced obesity via unrestricted access to a calorically dense high fat diet for 12 weeks in a randomly chosen subset of mice while the remaining mice were maintained on unrestricted access to a taste-matched control diet. We found that glutamatergic activity during sucrose consumption was suppressed following chronic exposure to high fat diet and that the depressed activity preceded dramatic weight gain. Using *ex vivo* electrophysiology, we confirmed that LHA glutamatergic neurons were less excitable following chronic high fat diet exposure. These data support a role for lateral hypothalamic glutamatergic neurons as a negative regulator of feeding.

Elevated activity of lateral hypothalamic glutamate cells is associated with a reduction in food intake, while increased caloric intake is associated with reduced neuronal activity.

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**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.13/PP4

**Topic:** F.10. Food Intake and Energy Balance

**Support:** R01 EB003268

**Title:** Transiently opening the blood-brain-barrier in the diagonal band of Broca using MR-guided focused ultrasound results in short-term reductions in weight gain

**Authors: *S. MOONEY**[1], K. HYNYNEN[2]
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**Abstract:** The diagonal band of Broca is a promising target for manipulating food intake and weight gain in rodents. Here, we used MR-guided focused ultrasound to manipulate this basal forebrain structure. Rats were treated with ultrasound to either transiently open the blood-brain-barrier or to cause minor edema in the area. Food intake and weight gain were then recorded for 5 weeks following treatment. Blood-brain-barrier disruption resulted in a decrease in weight gain 1 week after the treatment. This was true of young animals that gained large amounts of weight during the beginning of this experiment and of older animals that had reached a lower rate of weight gain. No effects were seen in food intake or activity levels. These results suggest that ultrasound-mediated disruption of the blood-brain-barrier results in a short-term decrease in weight gain persisting up to 1 week.

**Disclosures: S. Mooney:** None. **K. Hynynen:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

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**Program#/Poster#:** 510.14/PP5

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIDA

NIAAA

**Title:** Characterization of a novel ghrelin receptor knockout rat

**Authors: *L. J. ZALLAR**[1,3], B. J. TUNSTALL[1], Y. ZHANG[1,3], C. T. RICHIE[1], J. PICKEL[2], G. F. KOOB[1], L. F. VENDRUSCOLO[1], B. K. HARVEY[1], L. LEGGIO[1,3]
[1]NIDA, NIH, Baltimore, MD; [2]NIMH, NIH, Bethesda, MD; [3]NIAAA, NIH, Bethesda, MD

**Abstract:** Ghrelin is an appetitive hormone mainly produced by endocrine cells in the stomach. Ghrelin has been implicated in appetite, metabolism, stress, and more recently, in drug seeking. The growth hormone secretagogue receptor (GHSR) is the endogenous receptor for ghrelin, and it is expressed widely throughout the central nervous system and the periphery. The development of transgenic models would allow us to study the functional role of ghrelin signaling in physiology and behavior, which includes a role in homeostatic control of energy intake and obesity, and potentially, drug dependence. We sought to generate a novel GHSR knockout (KO) rat line through CRISPR/Cas9 mutation of the GHSR gene in a Wistar background. Using RNAscope, we confirmed the absence of GHSR expression in brain tissue. We also observed that GHSR-KO rats ate and weighed significantly less than wildtype (WT) rats. There were no group differences in locomotion, which suggests that the reduced body weight in GHSR-KO rats was a direct consequence of decreased food intake. Finally, GHSR-KO animals, compared to their WT littermates, were insensitive to food-intake promoting effects of a challenge dose of ghrelin. Together, the data suggest the successful development of a novel GHSR-KO rat that exhibits several features expected to result from GHSR knockout. This novel GHSR-KO rat model constitutes a useful tool for investigating the specific role of ghrelin signaling in physiology and behavior, which will be particularly important for defining the role of ghrelin signaling in addiction.
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**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.15/PP6

**Topic:** B.01. Neurotransmitters and Signaling Molecules

**Support:** NSF

**Title:** Genome-wide expression profiling in single identified interneurons of the feeding circuit as functions of the feeding arousal

**Authors: *E. C. DABE**[1], C. LEE[2], R. GILLETTE[3], L. L. MOROZ[4]
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**Abstract:** *Pleurobranchaea californica* is a powerful neuroethology model allowing us to assess fundamental links between gene expression, network excitability, and behavioral arousal all with single-neuron resolution. We sequenced identifiable single-neurons, whole CNS and 12 peripheral tissues to create an encompassing *Pleurobranchaea* hybrid reference transcriptome. *Pleurobranchaea* has distinctive food-seeking and avoidance behaviors dependent on its hunger state. These behaviors are controlled by the feeding network and partially modulated by a bilateral pair of giant serotoninergic metacerebral interneurons (MCCs). Analysis of indole metabolites in these MCCs has previously shown that satiated animals have reduced levels of serotonin (5-HT) and its metabolite 5-HT-$SO_4$ (but not of its precursor tryptophan or the metabolite 5-hydroxyindole acetic acid) 24 hrs post-feeding, compared to unfed controls. We collected extracellular recordings from the cerebral-buccal-connectives from *Pleurobranchaea* 24 hours post-feeding or unfed (n=6 per group) and found a decrease in spike frequency in satiated animals. Together the data suggest a reduction in synthesis and possibly in release of serotonin in satiated MCCs and also reduced firing activity of the MCCs. We investigated whether changes in RNA expression contribute to this phenotype by comparing single-neuron MCC transcriptomes from hungry and satiated animals (n=6 per group). RNA-seq data were mapped against the hybrid *Pleurobranchaea* transcriptome assembly. Normalized RNA expression levels in transcripts per million (TPM), and differential transcript expression were calculated using RSEM and DESEQ2. Preliminary data showed many differentially expressed genes. Satiated MCCs showed increased expression of the inhibitory neuropeptide PRQFVamide. Though previously implicated in feeding networks of *Aplysia californica*, PRQFVamide has not been shown to be expressed in MCCs before. Expression patterns of PRQFVamide were confirmed via *in situ* hybridization in satiated and hungry *P. californica* CNSs and in satiated *A. californica*. MRNA-binding proteins associated with sequestering and promoting translation of transcripts were upregulated in satiation and hungry animals respectively. These mRNA binding proteins could contribute to the changes in serotonin synthesis and release observed in *P. californica*. These finding suggests a potential new mechanism of post-transcriptional regulation of serotonin expression and a new role for an identified feeding network neuropeptide.Funding: NSF

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**Poster**

**510. Control of Feeding and Satiety**

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**Program#/Poster#:** 510.16/PP7

**Topic:** F.10. Food Intake and Energy Balance

**Support:** CAPES

Araucaria Fundation

**Title:** CRH-1 and CRH-2 receptors are involved in vasoactive intestinal peptide-induced hypophgia

**Authors: *M. C. GARNICA-SIQUEIRA**[1], A. B. MARTINS[1], D. M. ZAIA[2], C. B. V. ZAIA[1], E. T. UCHOA[1]
[1]Physiological Sci., [2]Chem., State Univ. of Londrina, Londrina, Brazil

**Abstract:** Vasoactive intestinal peptide (VIP) acts as an anorectic signal that inhibits food intake. VIP microinfusion in the paraventricular nucleus of the hypothalamus promotes plasma increase on the concentrations of glucose, free fatty acids, and corticosterone. The aim of this study was to evaluate the effects of VIP on the activation of neurons in the paraventricular nucleus of hypothalamus (PVN), and the effects of pretreatment with corticotrophin releasing hormone (CRH) receptor antagonist type 1, antalarmin (ANT), and type 2, antisauvagine (AS30), on food intake in response to intracerebroventricular (ICV) administration of VIP. Male Wistar rats (250-280 g) with 16h fasting received ICV microinjection (lateral ventricle, by stereotaxy, Paxinos and Watson) of AS30 (5 μg in 5 μL), ANT (0.25 μg in 5 μL) or vehicle, and after 15 minutes animals received VIP (40 ng/g in 6 μL) or saline (0.9% in 6 μL). After 15 minutes animals were fed and the amount of food intake was determined for 120 minutes. In another set of experiments, the animals received only VIP or saline ICV microinjection and after 90 minutes were intracardially perfused for Fos-related antigen (FRA) immunolabeling. In both protocols, cannula placement was histologically evaluated (CEUA No. 4929201580). Data were statistically analyzed by ANOVA two-way, followed by Student Newman-Keuls test (SNK) and T-test in results with normal distribution and homogeneity of variance, and significance level of $p<0.05$. VIP microinjection increased ($p<0.05$) the number of FRA-immunoreactive neurons in medial, ventral, and posterior parvocellular subdivisions of the PVN. As expected, VIP microinjection reduced ($p<0.05$) food intake in vehicle pretreated animals, but there was no effect on ANT pretreated group, which showed higher food intake than vehicle-VIP animals. In AS30 pretreated group, VIP microinjection reduced food intake, but this value was also higher than vehicle-VIP animals. These data indicate that central microinjection of VIP is able to activate parvocellular PVN neurons, in subdivisions with high expression of CRH neurons. Moreover, pretreatment with ANT reversed and AS30 partially reversed the reduction of food

intake induced by VIP, suggesting that VIP-induced hypophagia involves the activation of CRH neurons in the PVN, and thus both CRH-1 and CRH-2 receptors act as mediators of the central effects of VIP on energy homeostasis.

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**Poster**

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**Program#/Poster#:** 510.17/PP8

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIH R01DK012918

**Title:** Divergent effects of high fat diet on intrinsic and synaptic excitability in AgRP neurons

**Authors: *W. WEI**, C. KACZOROWSKI, K. M. S. O'CONNELL
Res., The Jackson Lab., Bar Harbor, ME

**Abstract:** In the arcuate nucleus of the hypothalamus (ARH), neurons co-expressing the neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY) are essential for driving food intake. Consistent with their role in regulating energy balance, their activity is tightly correlated with an animal's nutritional status, as increased activity is associated with food deprivation and decreased activity associated with satiety. AgRP neurons are modulated both by peripheral signals such as leptin and ghrelin as well as by synaptic inputs from glutamatergic and GABAergic circuits originating from other CNS regions. Our lab has recently demonstrated that AgRP neuronal excitability is sensitive to diet and body weight, implicating diet-induced plasticity of AgRP neurons as a causal factor in the development and maintenance of obesity. In this study, we found that the high-fat diet (HFD)-induced increase in AgRP neuronal excitability is persistent and does not reverse, regardless of the duration of HFD feeding, even after returning the mice to a low-fat diet for 2 months, suggesting that HFD induces a persistent remodeling of neuronal excitability, possibly including synaptic inputs. We hypothesized that HFD may induce an increase in excitatory synaptic input, with a concomitant decrease in inhibitory input, contributing to the overall increase in excitability in AgRP neurons following HFD. However, changes in synaptic activity did not mirror the change of the intrinsic firing rate. While fasting was associated with an increase in the frequency of excitatory postsynaptic currents (EPSCs) as expected, to our surprise, chronic HFD feeding had no significant impact on EPSC frequency.

Further, we observed no significant effect of fasting on the inhibitory postsynaptic current (IPSC) frequency, while HFD was associated with a significant increase in the frequency of IPSCs in AgRP neurons. Thus, HFD consumption may result in a failure of postsynaptic AgRP neurons to efficiently integrate incoming synaptic information and/or induce plasticity in the postsynaptic properties that determine excitability.

**Disclosures: W. Wei:** None. **C. Kaczorowski:** None. **K.M.S. O'Connell:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.18/PP9

**Topic:** F.10. Food Intake and Energy Balance

**Title:** Replacement of a high fat diet for healthier chow: Effects on explorative and anxiety-like behaviors

**Authors:** *I. K. MONTEIRO DEPINA[1], ***I. K. MONTEIRO DEPINA**[1], N. L. ARRUDA[1], R. R. GELINEAU[1], A. V. CUSHMAN[1], M. H. CHASSE[1], J. A. SEGGIO[2]
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**Abstract:** Over the decades in the United States, obesity has increased rapidly due to a decrease in nutritional benefits in food replaced by an increase in high fat and artificial glucose content, enabling many individuals to make poor diet choices. Similar to drug addictions, consumption of a high fat diet enables individuals to develop a dependency on the diet and undergo withdrawal effects like anxiety and overeating when a diet replacement occurs. This study focuses on whether change of diet can produce long term alterations to explorative and anxiety-like behaviors in male C57BL/6J mice. Mice were housed in a standard caging in a 12:12 light/dark cycle, with access to either a 60% high fat diet (high fat continuous HFC) or regular chow (RC) ad libitum. After six weeks on the high fat diet, all mice were subjected to the open field for five minutes and the light:dark box assay for ten minutes each to assess explorative and anxiety-like behaviors. Afterwards, one half of the mice fed high fat diet were switched to regular chow (high fat diet replacement HFR) for 3 weeks. After 3 weeks, mice were subjected to the same behavioral tests to assess possible long term changes to behavior - either a recovery of behavior to controls or possible long term withdrawal effects. Prior to the food switch, no differences were found amongst all the groups for the open field, but mice fed high fat diet (HFC and HFR) did exhibit reduced number of transitions within the light:dark box. After the food switch, HFC had reduced velocity, distance and rears than the high fat replacement group and regular chow controls, indicating decreased explorative behaviors in mice continuously fed a high fat diet. Mice continuously consuming high fat diet spent more time within the dark zone compared to mice with high fat diet replaced or regular chow controls, indicating increased anxiety in mice

fed high fat diets. In summary, mice continuously fed high fat diets exhibited increased anxiety and decreased explorative behaviors compared to regular chow controls and mice with high fat diet replaced with healthy chow. These results indicates that replacing a high fat diet with a lower caloric diet can produce a rebound effect which suggests that the behavioral deficits caused by high fat diet can be avoided by switching to a healthy diet.

**Disclosures: I.K. Monteiro Depina:** None. **N.L. Arruda:** None. **R.R. Gelineau:** None. **A.V. Cushman:** None. **M.H. Chasse:** None. **J.A. Seggio:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.19/PP10

**Topic:** F.10. Food Intake and Energy Balance

**Support:** UNAM DGAPA IN217117

**Title:** Activation of CB2 receptors in the nucleus accumbens shell stimulates palatable food ingestion in pre-satiated rats

**Authors: *R. ESCARTIN-PEREZ**[1], F. CORTÉS-SALAZAR[1], M. HERNÁNDEZ-GAVIÑO[1], V. LÓPEZ-ALONSO[1], A. HERNÁNDEZ-GUTIÉRREZ[2], J. MANCILLA-DIAZ[1]
[1]UNAM, FES Iztacala, Tlalnepantla de Baz, Mexico; [2]Inst. Politécnico Nacional, Ciudad de México, Mexico

**Abstract:** Despite obesity have multifactorial causes, recurrent over-consumption of energy-dense foods is a common feature of these patients. Energy-dense diets are usually highly palatable and activate the brain reward circuit, promoting over-consumption of food. It is generally accepted that endocannabinoid system plays a key role in the regulation of energy homeostasis and food intake regulation, and activation of CB1 receptors in the NAcS consistently stimulate food intake. However, recent reports have provided evidence implicating brain CB2 receptors in modulating a CNS functions. For instance, activation of brain CB2 receptors in mice inhibited both the behavioral and neurochemical effects of cocaine, suggesting that CB2 receptors functionally modulate the mesolimbic DA system and DA-related functions. Accordingly, we propose the hypothesis that the activation of cannabinoid CB2 receptors in the in the NAcS affect the processing of hedonic properties of palatable food. Thus, the aim of this study was to evaluate the effect of administration of the selective CB2 receptor agonist, GW-405833, in the NAcS on palatable food intake in pre-satiated rats. Male Wistar rats were anesthetized and were stereotaxically implanted with unilateral guide cannulas for injection into the NAcS and had a 5-day recovery period. Then, during a 7-day period of habituation, rats (220-240g) were deprived of food for 21 hours, and then they had access to the standard food (solid)

during 2 hours, and finally they had access to the experimental food (sweetened condensed milk, 10% sucrose) for 1 hour during the light phase of the light/dark cycle. This procedure was performed in order to guarantee that animals were pre-satiated at the time of access to the palatable food, consuming it by its palatability properties. Body weight was monitored on a daily basis to ensure animals continued growing and were appropriately adapted to the food-restricted paradigm. In the experimental sessions, the animals were injected with vehicle and different doses of GW-405833 (0.25, 0.5 or 1.0 μg, multidose crossover design, where dose was determined by a Latin square with an inter-test interval of 2 days, each rat was registered in 3 independent experimental sessions) before having access to experimental food (rats were in the same feeding paradigm as in the habituation period). According to our results, GW-405833 administration had a dose-dependent stimulatory effect of palatable food ingestion. Our findings provide experimental evidence that cannabinoids and endocannabinoids in the NAcS may stimulate feeding by increasing the hedonically positive sensory properties of food via CB2 receptors.

**Disclosures:** **R. Escartin-Perez:** None. **F. Cortés-Salazar:** None. **M. Hernández-Gaviño:** None. **V. López-Alonso:** None. **A. Hernández-Gutiérrez:** None. **J. Mancilla-Diaz:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.20/PP11

**Topic:** F.10. Food Intake and Energy Balance

**Support:** Kakenhi 23390044

**Title:** Nucleobindin-2/nesfatin-1 in the hypothalamic paraventricular nucleus is regulated by metabolic factors

**Authors: *D. GANTULGA**[1], Y. MAEJIMA[2], M. NAKATA[2], T. YADA[2]
[1]Dept. of Basic Sci., Sch. of Pharm. and Biomedicine, Natl. Unive, Ulaanbaatar, Mongolia; [2]Physiol., Jichi Med. Univ., Shimotsuke, Japan

**Abstract:** Nesfatin-1, an anorectic peptide processed from nucleobindin-2 (NUCB2), is an emerging new player in regulation of food intake and energy metabolism. NUCB2/nesfatin-1 is localized in the hypothalamus including paraventricular nucleus (PVN), the region serving as an integrative center for energy homeostasis. Extensive studies on the neural pathways downstream of PVN NUCB2/nesfatin-1 have shown a pivotal role of oxytocin and corticotropin-releasing hormone. In contrast, the factors that regulate NUCB2/nesfatin-1 neurons in PVN remain unknown. This study aimed to clarify whether high glucose, insulin and leptin could directly activate NUCB2/nesfatin-1 neurons in the PVN, and whether the NUCB2/nesfatin-1 expressing

in PVN mediates anorectic action of leptin.Glucose (10 mM) and insulin (10-13 M) increased $[Ca^{2+}]_i$ in 55 of 331 (16.6%) and 32 of 249 (12.9%) PVN neurons, respectively. The post $[Ca^{2+}]_i$ measurement immunocytochemistry indicated that 32 of 55 (58%) glucose-responsive neurons and 20 of 32 (63%) insulin-responsive cells were NUCB2/nesfatin-1 neurons. Substantial fraction of glucose-responsive NUCB2/nesfatin-1 neurons in the PVN also responded to insulin and vice versa. In addition, leptin (10-11 M) increased $[Ca^{2+}]_i$ in 44 of 208 (21.2%) PVN neurons, and 30 of 44 (68.2%) the leptin-responsive neurons were identified as nesftin-1 neurons. These results indicate that high glucose, insulin and leptin activate the PVN NUCB2/nesfatin-1 neurons. Furthermore, central injection of leptin significantly increased NUCB2 mRNA expression in vivo, and treatment of isolated PVN slices with leptin in culture increased NUCB2 mRNA expression. In mice injected with AAV-NUCB2-shRNA, both central and peripheral leptin injection failed to inhibit food, indicating that PVN NUCB2 serves as a substantial mediator of leptin action in PVN. In conclusion, high glucose, insulin and leptin are upstream regulators of PVN NUCB2/nesfatin-1 and PVN NUCB2/NUCB2/nesfatin-1 neurons at least partly mediate the leptin signaling for inhibiting feeding. This study contributes to our understanding of regulation of PVN NUCB2/nesfatin-1 and highlights the role of PVN NUCB2 in energy homeostasis.

**Disclosures: D. Gantulga:** None. **Y. Maejima:** None. **M. Nakata:** None. **T. Yada:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

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**Program#/Poster#:** 510.21/PP12

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIH MS-PhD Bridge Grant R25-GM048972

**Title:** Biogenic amine octopamine attenuates effects of acute starvation and environmental stress in the house cricket (acheta domesticus)

**Authors: *G. M. DOWNING**, B. ARRIAGA, K. A. ALEGRETE, C. A. MOFFATT
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**Abstract:** Environmental complexity and caloric restriction have been shown to alter neurogenesis in vertebrate species; however, their effects in arthropods remain poorly understood. In our lab, we utilize a novel organism, Acheta domesticus (the house cricket) to study neurogenesis. We have found neurogenesis is increased in adult crickets housed in enriched environments and decreased in those housed impoverished environments. We also found that acute starvation decreases neurogenesis. Interestingly, we also found that neurogenesis persisted at high rates in crickets even when they were housed in impoverished

conditions and starved at the same time, suggesting that crickets maintain a commitment to maintaining neurogenesis even in extremely stressful conditions. Our goal in the current experiments was to determine if the neuromodulatory hormone octopamine (OA) plays a role in mediating the changes in the rate of neurogenesis we see in stressful conditions. OA is critical for lipid synthesis, and stimulates insulin-producing cells in the mushroom bodies, a region of the brain where neurogenesis occurs in adult crickets. We hypothesized that decreases in OA activity contribute to the decrease in neurogenesis in environmentally impoverished and calorically restricted conditions. To test this hypothesis, we housed crickets in an impoverished environment and acutely starved them for 96 hours. All crickets had access to water for the duration of the experiment. Following 96 hours, crickets received a 10µL injection containing 5µL BrdU (20mg/mL), a thymidine analog incorporated into DNA during the S-phase of the cell cycle, and 5µL of a 50 mM, 100mM, or 200mM solution of OA, or with 5µL of saline. Two hours later, the crickets were sacrificed and their brains were processed for detection of BrdU immunoreactivity. Relative to saline-injected controls, the number of BrdU-immunoreactive cells was increased in crickets injected with 50 and 100 mM OA ($p < .01$) but not in crickets injected with 200 mM OA ($p > .05$). These data suggest OA upregulates neurogenesis in crickets housed in impoverished environments. Preliminary data from another study suggests OA has similar effects in enriched environments. Future studies will examine the effects that OA antagonists have on neurogenesis in impoverished and enriched environments.

**Disclosures: G.M. Downing:** None. **B. Arriaga:** None. **K.A. Alegrete:** None. **C.A. Moffatt:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

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**Program#/Poster#:** 510.22/PP13

**Topic:** F.10. Food Intake and Energy Balance

**Support:** DK104897

**Title:** Gastrointestinal vagal afferent signaling promotes hippocampal-dependent memory function in rats

**Authors: *A. N. SUAREZ**[1], T. M. HSU[1], G. DE LARTIGUE[2], S. E. KANOSKI[1]
[1]USC, Los Angeles, CA; [2]John B. Pierce Lab., Yale Univ., New Haven, CT

**Abstract:** The vagus nerve is the primary conduit of communication between feeding-relevant gastrointestinal (GI) signals and the brain. Vagally-mediated GI satiation signals, including gastric distension and intra-gastric nutrient infusion, activate neurons in the hippocampus (HPC) through unidentified polysynaptic pathways. The functional relevance of GI-derived

communication to the HPC is unknown. Here we first explored whether chronic disruption of gut-to-brain vagal tone via subdiaphragmatic vagotomy (SDV) negatively impacts HPC-dependent memory function in rats. While SDV did not impair HPC-dependent appetitive learning based on interoceptive energy status cues or social food-related cues, SDV did impair spatial working memory (Barnes maze) and contextual episodic memory (novel object in context; NOIC), two HPC-dependent tasks that involve processing of visuospatial stimuli. Next, to determine whether vagal sensory/afferent vs. motor/efferent signaling regulates HPC-dependent memory function, we employed a novel approach in which a saporin conjugated to cholecystokinin (CCK-SAP) or an unconjugated control saporin is injected into the nodose ganglia, a strategy that preserves 100% of vagal efferent signaling while eliminating ~80% of GI-derived vagal afferent signaling. Similar to SDV rats, CCK-SAP rats were impaired in both the Barne's maze task and NOIC learning relative to controls. Consistent with the memory deficits, immunoblot protein analyses in hippocampus lysates revealed reduced neurotophic [brain-derived neurotrophic factor (BDNF)], and neurogenesis [doublecortin (DCX)] markers in both SDV and CCK-SAP rats relative to controls. These findings indicate that GI-derived vagal afferent signaling is critical in regulating HPC-dependent mnemonic function. Results have direct clinical relevance, as procedures that chronically disrupt vagus nerve signaling (e.g., vBloc) have recently been FDA-approved for obesity treatment.

**Disclosures:** **A.N. Suarez:** None. **T.M. Hsu:** None. **G. De Lartigue:** None. **S.E. Kanoski:** None.

**Poster**

**510. Control of Feeding and Satiety**

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**Topic:** F.10. Food Intake and Energy Balance

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Läkarutbildning och Forskning (ALFBGB-138741)

BBSRC

**Title:** Ghrelin conditions an avoidance in rodents

**Authors: *S. L. DICKSON**[1], C. COOK[2], S. M. LUCKMAN[2], E. SCHELE[1]
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**Abstract:** Feelings of hunger carry a negative valence (emotion) signal that appears to be conveyed through agouti-related peptide (AgRP) neurons in the hypothalamic arcuate nucleus1. The circulating hunger hormone, ghrelin, activates these neurons although it remains unclear whether it also carries a negative-valence signal. Given that ghrelin also activates pathways in the midbrain that are important for reward, it remains possible that ghrelin could act as a positive reinforcer and hence, carry a positive-valence signal. Here we used condition preference/avoidance tests to explore the reinforcing/aversive properties of ghrelin, delivered by intracerebroventricular (ICV) injection (2 µg/injection once a day for 4 days). We found that ICV ghrelin conditioned avoidance, both in a conditioned place preference/avoidance test (CPP/CPA, in which the animals avoid a chamber previously paired to ghrelin injection) and in a conditioned flavor preference/avoidance test (CFP/CFA, in which the animals consume/avoid a taste previously paired to ghrelin injection). These effects of ghrelin to induce a CPA were observed when conditioning to ghrelin occurred in the absence of food (77% reduction in time spent in ghrelin-paired compartment, $P<0.001$) and presence of food (in this case an 82% reduction; $P<0.001$). We did not find evidence, however, that brain ghrelin delivery to rats induces malaise (in the pica test). After conditioning, the preference for the flavor that had been conditioned to ICV ghrelin injection (31 ± 7 %) was dramatically reduced by over half ($P < 0.001$) compared with the initial preference (71 ± 3 %), which was determined prior to conditioning. Our data indicate that ICV ghrelin carries a negative-valence signal consistent with its role as a circulating hunger hormone and with its effects to activate AgRP neurones.1 Betley JN et al., Nature. 2015 521:180-5.

**Disclosures:** **S.L. Dickson:** None. **C. Cook:** None. **S.M. Luckman:** None. **E. Schele:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.24/PP15

**Topic:** B.09. Physiological Properties of Neurons

**Support:** NIDA/NIH

**Title:** Glutamatergic fast-spiking parvalbumin neurons in the lateral hypothalamus regulate feeding

**Authors: *A. KISNER**[1], J. E. SLOCOMB[1], S. SARSFIELD[1], J. F. GUPTA[1], A. KUMAR[2], Y. APONTE[1,3]
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**Abstract:** The cytoarchitecture and synaptic organization of neuronal circuits that control feeding behaviors play fundamental roles in regulating homeostatic control of the body. Beginning with early lesion and electrical stimulation studies, the lateral hypothalamus (LH) has long been considered essential in regulating feeding. In addition, the profusion of genetically distinct cell types in the LH make it an ideal circuit to study the neuronal basis of survival behaviors. However, very little is known about which cell types and relevant projections are important for driving and controlling feeding. In this work, we characterized and determined the role of lateral hypothalamic parvalbumin-expressing neurons ($LH^{PV}$) in regulating feeding behaviors in mice. These neurons (340 ± 10, $n$ = 3 mice; bilateral) are distributed in a compact and small cluster in the LH medial to the optic tract. Using a combination of electrophysiology, optogenetics, and *in situ* hybridization assays, we determined that $LH^{PV}$ neurons are fast-spiking (mean firing frequency 194 ± 10 Hz, $n$ = 34 cells), co-express vesicular glutamate transporter 2 (*Vglut2*) mRNA (95% $LH^{PV+/VGLUT2+}$), and provide excitatory inputs onto neuronal circuits within the LH (mean excitatory postsynaptic current (EPSC) amplitude 69.0 ± 5.0 pA, $n$ = 13 cells). This contrasts with the canonical parvalbumin neuron fast-spiking GABAergic phenotype observed in the neocortex and hippocampus. Furthermore, we manipulated the activity of $LH^{PV}$ neurons using chemogenetic techniques to determine whether these neurons are necessary and sufficient to drive feeding behaviors. We found that chemogenetic inhibition of $LH^{PV}$ neurons evoked food intake in sated mice (60% increase in food consumption in comparison to control; $n$ = 12). In contrast, chemogenetic activation of these neurons did not affect food intake ($n$ = 8). Thus, our results indicate that inhibitory inputs onto $LH^{PV}$ neurons orchestrate feeding behaviors. This study sheds light on the importance of understanding the functional roles of specific cell types within the LH in coordinating complex behaviors such as feeding. Additionally, elucidating the mechanisms regulating food intake will allow the identification of novel targets for therapies of metabolic disorders.

**Disclosures:** **A. Kisner:** None. **J.E. Slocomb:** None. **S. Sarsfield:** None. **J.F. Gupta:** None. **A. Kumar:** None. **Y. Aponte:** None.

**Poster**

**510. Control of Feeding and Satiety**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 510.25/PP16

**Topic:** F.10. Food Intake and Energy Balance

**Support:** Faculty start-up

**Title:** Alternate day fasting schedule in rats decreases preference for calorically dense diet by increasing meal size and number of meals of standard chow

**Authors: *M. FRANKOT**, A. CARRILLO, Y. TREESUKOSOL
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**Abstract:** Alternate day fasting (ADF), a paradigm involving free access to food for 24 hours followed by no access to food for 24 hours, leads to weight loss for both humans and rats. When rats receive ad libitum access to both a palatable high-energy (HE) food and standard chow they tend to overeat HE food and gain weight. In order to examine how fasting alters diet preference and intake, meal pattern analysis was conducted across daily 23-h sessions in male and female Sprague Dawley rats. Animals were assigned to one of three diet conditions: AD LIB rats were given access to both chow (3.43 kcal/g) and HE diet (4.73 kcal/g) every day, INT rats were given access to chow every day with the addition of HE diet every other day, and ADF rats were given access to both chow and HE diet every other day; no food was administered on alternate days. Given the 24-h food restriction periods, it was anticipated that ADF rats would show the highest preference for HE food versus chow, yet the ADF group displayed decreased preference for HE compared to INT and AD LIB rats ($p < .001$). This effect was more pronounced in male rats than in female rats. Consistent with findings in the literature, access to a palatable caloric-dense diet in a fed state (INT rats) resulted in hyperphagia driven by increased meal size of the HE diet ($p = 0.008$). This was not observed in ADF rats that were presented HE diet and chow following 24-h food restriction. The decreased preference for HE diet in ADF rats appears to be driven by changes in meal pattern parameters. Specifically compared to the INT group, ADF rats initiated more meals ($p < 0.001$) and displayed larger meal size ($p = .035$) of chow. The direct controls of meal size can be categorized as positive (e.g., oral) and negative (e.g., postoral inhibitory) signals; thus here, the ADF schedule appears to increase orosensory stimulation and/or decrease sensitivity to inhibitory cues towards the less-preferred chow. This shift in diet preference may contribute to the effectiveness of using ADF as a dieting strategy.

**Disclosures: M. Frankot:** None. **A. Carrillo:** None. **Y. Treesukosol:** None.

**Poster**

**510. Control of Feeding and Satiety**

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**Topic:** F.10. Food Intake and Energy Balance

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Burroughs Wellcome Trust

**Title:** Reward sensitivity deficits in rats following intermittent access to a palatable diet

**Authors: *C. F. MOORE**, V. SABINO, P. COTTONE
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**Abstract:** Eating disorders and forms of obesity are associated with brain reward dysfunction. In this study we investigated the sensitivity of the brain reward system of subjects undergoing chronic diet cycling by testing the effects of *d*-Amphetamine, a dopamine releaser. For this purpose, a group of male Wistar rats was provided a regular chow diet 7 days a week (*Chow/Chow*), whereas a second group of rats was provided chow for 5 days a week, followed by a 2-day access to a highly palatable sucrose diet (*Chow/Palatable*). Following 5 weeks of diet alternation, we investigated *d*-Amphetamine sensitivity during access to the palatable diet (*'P Phase'*) as well as during withdrawal from it (*'C Phase'*). We measured the effect of d-Amphetamine on locomotor activity and brain stimulation reward (BSR), home-cage self-administration of amphetamine, and *d*-Amphetamine-induced conditioned place preference. In addition, we used quantitative polymerase chain reaction (qPCR) to investigate diet-induced molecular neuroadaptations. Palatable diet cycling resulted in hypophagia of the standard chow, overeating of palatable food upon renewed access, and compulsive-like eating. During the *P*, but not the *C phase*, diet cycled rats showed decreased sensitivity to both the locomotor stimulating and the threshold-reducing effects of *d*-Amphetamine. The rewarding effects of *d*-Amphetamine were also reduced in *Chow/Palatable* rats during the *P Phase*, shown by blunted place conditioning. In addition, during access to the palatable diet, *Chow/Palatable* rats showed increased self-administration of *d*-Amphetamine in the home cage, as compared to controls. Furthermore, we found that intermittent access to a palatable diet altered expression of dopamine signaling targets. These results indicate that diet cycled rats show a phase-dependent deficit in the brain reward system, as revealed by a decreased sensitivity and reward to *d*-Amphetamine, as well as increased self-administration of *d*-Amphetamine when the highly palatable food access is renewed following withdrawal from the diet. In summary these results suggest that, in pathological eaters, brain reward dysfunction may be dependent upon the feeding state of the individuals.

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**Poster**

**510. Control of Feeding and Satiety**

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**Topic:** F.10. Food Intake and Energy Balance

**Support:** Mayo Clinic CIM

Mayo Clinic Graduate School of Biomedical Sciences

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P50AG016574

**Title:** The function of hypothalamic microRNA in regulating energy homeostasis

**Authors: *H. YOON**[1,2], T. WHITE[3], P. ZHANG[3], A. KURTI[2], J. D. FRYER[1,2], N. K. LEBRASSEUR[3], J. KIM[1,2]
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**Abstract:** Hypothalamus is a primary regulator of homeostasis in the whole body. It links the nervous system to the endocrine system. In particular, the arcuate nucleus (ARC) in hypothalamus controls energy homeostasis. For example, ARC plays important roles in regulating food intake and energy expenditure in response to hormones such as insulin and leptin, released from peripheral organs. In our study, we focused on the function of microRNAs (miRNAs) in hypothalamus as one of the potential regulators of energy metabolism. miRNAs are small non-coding RNAs that regulate posttranscriptional gene expression. They play critical roles in various biological processes and dysregulations of miRNAs are associated with pathogenesis of multiple human diseases.
We performed miRNA profiling from different mouse brain sub-regions and found that a particular miRNA is significantly enriched in hypothalamus, particularly in ARC. Given its unique expression pattern, we hypothesized that the miRNA may regulate neuronal functions specific in hypothalamus. Microarray analysis indicated that the overexpression of this particular miRNA in neuronal cell dramatically affects metabolic processes and lipid transport processes. We also found that overexpression of this miRNA reduces the level of phosphorylated serine/ threonine-specific protein kinase AKT (AKT) and glycogen synthase kinase 3 β (GSK3β) in hypothalamic cell line. Interestingly, insulin signaling pathway mediated by AKT and GSK3β is one of the main regulators of energy homeostasis in hypothalamus. In this context, we further investigated the function of this miRNA in the hypothalamus of wild-type B6 mice under the normal diet and high fat diet feeding condition. Dysregulation of this miRNA in the brain disturbed the energy balance of the whole body and glucose metabolism. This study may help understand the pathophysiological mechanisms of obesity and diabetes.

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**Poster**

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**Program#/Poster#:** 510.28/PP19

**Topic:** F.10. Food Intake and Energy Balance

**Support:** Swiss Anorexia Nervosa Foundation

Olga Mayenfisch Stiftung

**Title:** A Neuronal circuit for the response to hypoglycemia in the insular cortex

**Authors: *I. DE ARAUJO SALGADO**, N. BENFREDJ, C. M. LAMY
Univ. of Fribourg, Fribourg, Switzerland

**Abstract:** Given the importance of glucose for the brain, the glycemic level is highly monitored by the central nervous system. A drop in blood glucose level triggers vital behavioral changes to insure survival. Using whole-cell recording, we have previously identified the existence of glucose-sensing cells in the insular cortex (IC), a region involved in interoception and adaptive behaviors. We are now investigating the neuronal circuit associated with those neurons and their behavioral function. Using a transgenic activity reporter mouse model, we confirmed the presence in IC of hypoglycemia-activated neurons in vivo. We then investigated the role of those neurons in adaptive behaviors by re-activating them in vivo. Our study demonstrates the existence of a neuronal circuit in IC implicated in behavioral adaptation to hypoglycemia.

**Disclosures: I. De Araujo Salgado:** None. **N. BenFredj:** None. **C.M. Lamy:** None.

**Poster**

**511. Striatal Circuits in Behavior**

**Location:** Halls A-C

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** Attilio Iemolo, PhD Career Integration Grant for Excellence from 'Fondazione con il Sud' (2011-PD-13)

**Title:** Unraveling the discrete and cooperative game between the prefrontal cortex and striatum in the modulation of working memory capacity in mice

**Authors: *A. IEMOLO**[1,2], E. C. LATAGLIATA[3], A. ARPINO[2], S. PUGLISI-ALLEGRA[3], E. DE LEONIBUS[2,4]
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**Abstract:** Working memory capacity (WMC), also known as memory span, can be defined as the maximum number of items one can hold in working memory. WMC is between 5 and 9 and is assumed to be a system involving both short-term memory and executive functions. WMC declines as a result of aging, neuropsychiatric conditions and may be a marker of early onset of Alzheimer's and Parkinson's disease. The prefrontal cortex (PFC) is implicated in supporting WMC, and its connections to the striatum are considered a major pathway in transforming plans into action. In this context, it has been proposed that WMC in humans can be associated with dopaminergic (DAergic) activity in the PFC either directly, through DAergic mesocortical input, or through striato-thalamocortical innervations modulated by the DAergic nigrostriatal pathway. However, whether and how a selective damage of either the PFC or the dorsal striatum (DS), affects WMC performance in rodents, still requires exploration. Additionally, whether an intact interaction between these two brain structures is necessary for a correct WMC performance, lacks experimental evidence. Therefore, in the current study, CD1 mice received bilateral 6-OHDA lesions either in the medial PFC (mPFC) or DS. A separate group of animals received, instead, crossed lesions of the DS, in one hemisphere, and the mPFC in the other. Two weeks after intra-brain injection, all animals were screened for WMC, using a modified version of both the novel object recognition test (6-DOT, six different object task) and the radial maze test, exposing mice to both low- and high-memory load protocols. Our results demonstrate that when lesions selectively affect the mPFC, a profound deficit in object WMC is observed. However, no impairments in WMC were found in the modified version of the radial maze. On the other hand, DAergic depletion in the DS, although leading to increased time spent in exploring the objects, did not result in object WMC deterioration. In spite of that, an increase in the mean error numbers in the radial maze test was registered when a high-memory load paradigm was applied. Interestingly, mice with crossed lesions showed both a slight reduction in object WMC and an increased mean error numbers in the radial maze test. Thus, these data demonstrate that the mPFC and the DS specialize in different aspects of WMC and suggest that functional connectivity between them is necessary to support diverse representation of WMC. Elucidating the precise neural mechanisms underlying WMC would advance our understanding of WMC-dependent cognitive and behavioral capabilities, as well as provide clues to the pathophysiology and treatment of WMC deficits in pathological states.

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**Poster**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH grant P50NS091856

**Title:** Disruption of the ability of cues to direct movements following silencing of striatal cholinergic interneurons

**Authors: *C. AVILA**[1], A. J. KUCINSKI[1], M. SARTER[2]
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**Abstract:** Falls in patients with Parkinson's disease (PD) are correlated with cholinergic but not with striatal dopaminergic losses. Such falls are thought to reflect in part a loss of attentional compensatory supervision of slow and low-vigor movement. Forebrain cholinergic systems normally mediate the detection and processing of exteroceptive and interoceptive cues, including balancing and movement errors. Such information is forwarded to the striatum to guide and correct forward movements, specifically in unfamiliar contexts and involving dynamic surfaces. Following cholinergic losses, the striatum is deprived of such information which, in interaction with slow and low-vigor movement resulting from striatal dopamine losses, yields balancing and movement errors that precipitate falls. We hypothesize that striatal cholinergic interneurons integrate cortical, cue-related input with information related to ongoing movement in the striatum mediated by dopamine. This hypothesis implies that silencing of interneuron function disrupts the ability of cues to direct movements. Here we tested this hypothesis by activating an inhibitory DREADD, expressed bilaterally by dorsomedial striatal cholinergic interneurons, in animals which had been trained to respond to two cues, a tone or light. The "stop cue" instructs the animals to stop treadmill walking and then continue walking after three seconds in the same direction when the treadmill restarts, whereas with the "turn cue" animals learn to stop, turn around, and walk in the reverse direction. The effects of clozapine N-oxide (CNO; 5 mg/kg; i.p.) or vehicle were tested four weeks after DREADD infusions into the striatum. Preliminary findings indicate that CNO administration disrupts the efficacy of the turn cue response while stop-cue-evoked behavior remained unaffected. Control tests confirmed that administration of CNO neither disrupted the animals' ability to turn *per se* nor induced a preferred turning direction. These results support the hypothesis that striatal cholinergic interneurons mediate the integration of cues into complex movement sequences such as turning. Related research will test the hypothesis that the cortico-striatal, glutamatergic transfer of cue information is disrupted following forebrain cholinergic losses. Collectively, this research suggests that new treatments

aimed at restoring cortico-striatal signaling via striatal cholinergic interneurons may facilitate the integration of afferent information originating in cortical and midbrain regions and thus reduce falls in PD patients.

**Disclosures: C. Avila:** None. **A.J. Kucinski:** None. **M. Sarter:** None.

**Poster**

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**Support:** EMBO long-term fellowship

ONR

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**Title:** Ventral striatum predicts reward during operant neuroprosthetic learning task

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**Abstract:** It has been shown that animals can learn to generate arbitrary patterns of neural activity in the frontal and motor cortices in the context of abstract skill learning, such as operant neuroprosthetic learning tasks, and that this learning undergoes plastic changes in the dorsal striatum as well as cortico-striatal interactions. However, the role of the ventral striatum (VS) during abstract skill learning remains unclear.
Here we investigated interactions between the VS and primary motor cortex (M1) while rats learned to modulate M1 activity to control a one-dimensional auditory cursor that was linked to a sucrose water reward. Animals learned to perform the task above chance level, and become skilled through training. VS firing rates around the time of target hit increased during this learning process, suggesting that the VS is modulated by reward prediction stimuli. These results are consistent with the actor-critic model of reinforcement learning and suggests an evaluative role of the VS during abstract skill learning.

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**Poster**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** Whitehall Foundation

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**Title:** A novel functional role for local striatal inhibitory circuits in goal-directed behavior

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**Abstract:** Deficits in goal-directed behavior are the hallmark of many neuropsychiatric diseases. The dorsomedial striatum (DMS) is a key mediator of goal-directed actions, serving as a critical node for integration of sensorimotor, motivational, and cognitive information. The local striatal low-threshold-spiking (LTSI) interneuron population is sparse, yet exhibits strong synaptic control over spiny projection neurons. Therefore, LTSIs are poised to play a key role in regulating goal-directed behavior. To provide initial evidence for LTSI involvement in operant behavior, we virally overexpressed Kir2.1, an inwardly rectifying potassium channel, to decrease excitability of LTSIs in the DMS. After one week of viral expression, mice were trained in a self-initiated operant task consisting of temporally discrete initiation, choice and outcome valuation periods. The task consisted of three phases: 1) Initiation: sustained entry in a central port initiated a trial, and two retractable levers extended. 2) Choice: mice must respond on one of the levers within 10s, otherwise the trial was considered an omission. 3) Outcome valuation: levers retracted and appropriate outcome was delivered. Responding on the active lever resulted in 4s illumination of the central port and delivery of 10 ul chocolate liquid reward, while responding on the inactive lever resulted in 4s darkness. After 1s time out, mice were allowed to initiate a new trial. To test initial action-contingency acquisition, mice were trained in a two-alternative forced choice task to respond on one lever. After 3 consecutive days >50 rewards, the contingency reversed, thereby rewarding the previously inactive lever. Mice were subsequently run in a dynamic serial reversal task, in which the active lever reversed after 8/10 correct responses. Reduced activity of LTSIs resulted in enhanced acquisition of the initial contingency, decreased the number of trials to reverse in the initial single reversal, and improved performance on the first day of the serial reversal task. To further explore the temporal specificity of LTSI involvement in this task, we used halorhodopsin-mediated optogenetic inhibition specifically during the outcome valuation phase. Similar to Kir2.1 overexpression, optogenetic inhibition of LTSIs exclusively during reward delivery accelerated task acquisition. Together, these data suggest striatal LTSI activity during reward processing may inhibit acquisition of new behavioral

contingencies. Current work is focusing on the striatal circuit mechanisms by which this interneuron population modulates goal-directed choice.

**Disclosures: E.N. Holly:** None. **M.F. Davatolhagh:** None. **K. Choi:** None. **M.V. Fuccillo:** None.

**Poster**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NEI Intramural

**Title:** Visual function of the putamen tail: Stable choice of valuable objects

**Authors: *O. HIKOSAKA**, J. KUNIMATSU
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**Abstract:** The basal ganglia, especially the circuits originating from the putamen, are essential for controlling normal body movements. Notably, the putamen receives inputs not only from motor cortical areas but also from multiple sensory cortices. However, how these sensory signals are processed in the putamen remains unclear. We recorded neuronal activity in the caudal part of the putamen when the monkey viewed many fractal objects. Among 63 neurons, 45 responded to the visual objects. A majority of them (40/45, 89%) had receptive fields in the contralateral hemifield. We hypothesized that these neurons changed their visual responses based on the reward outcome, because the putamen receives heavy dopaminergic inputs, as the other parts of the striatum.
To test this hypothesis, we first used a flexible value procedure in which the object-reward contingency was reversed in a block-wise manner. Among 28 visual neurons tested, only 2 showed differential responses based on the expected values. Next, we used a stable value procedure. In this task, the monkey viewed many fractal objects, each of which was followed by a big or small reward, consistently many times. After learning, the monkey tended to look at high-valued (good) objects and avoided low-valued (bad) objects, and did so with no reward outcome (i.e., free viewing), even a long time later (e.g., >1 month). We found that many of the visual neurons responded stably to these ‘good’ and ‘bad’ objects differentially. Such stable value responses were more common in the caudal-ventral part of the putamen (cvPut,12/24, 50%) than in the caudal-dorsal part (cdPut, 5/25, 20%). On the average, the response was stronger to good objects than bad objects in cvPut neurons ($p < 0.01$), but not cdPut neurons ($p = 0.36$). In addition, object-selective neurons were more common among cvPut neurons (15/24, 63%) than cdPut neurons (5/25, 20%). The magnitude of the object selectivity, on the average,

was stronger in cvPut than cdPut ($p < 0.05$). These results indicate that cvPut and cdPut process visual information differently.
Our recent study revealed that cvPut shares its outputs (Amita et al, SfN abstract 2016) with the tail of the caudate nucleus (CDt). CDt and its downstream circuit to the superior colliculus contribute to the automatic choice and rejection of visual objects based on the long-term memory of the object value (Hikosaka et al. Annu Rev Neurosci 2014). Therefore, cvPut would play the same role (i.e., choice by eye movement) and possibly an additional role (e.g., choice by hand). Anatomically, CDt and cvPut, together, can be called 'striatum tail'. However, the function of cdPut is still unknown.

**Disclosures: O. Hikosaka:** None. **J. Kunimatsu:** None.

**Poster**

**511. Striatal Circuits in Behavior**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NEI Intramural

**Title:** Visual function of the putamen tail: Flexible switching of object choice

**Authors: *J. KUNIMATSU**, O. HIKOSAKA
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**Abstract:** We found that neurons in the caudal-ventral part of the putamen (cvPut) encode values of visual objects stably, similarly to caudate tail (CDt) (Hikosaka and Kunimatsu, SfN abstract 2017). Such stable value coding would be useful for automatically and quickly choosing good objects among many others (Hikosaka et al. Trends Cogn Sci 2013). Our new experiment suggests that such stable value coding may also play a key role in flexible switching of object choice, as shown below.
We devised a new value procedure: scene-based value task. The monkey viewed 8 fractal objects in 2 scenes (A and B), repeatedly across days; 4 of them were good (with large-reward) in scene A and bad (with small-reward) in scene B, while the other 4 were good in scene B and bad in scene A. After experiencing this procedure repeatedly (> 5 days), the monkey became able to choose whichever objects were good. Since scenes A and B were presented in a random sequence, the monkey's choice was switched abruptly depending on the scene-context. Moreover, the flexible switching occurred even in the free viewing condition in which no reward was given after the choice.
We then recorded neuronal activity in cvPut while the monkey passively viewed these objects in different scenes. Most neurons in cvPut were visually sensitive and often encoded object values

stably. We found differences between medium spiny neurons (MSNs) and presumed inhibitory interneurons (INs). Among 33 MSNs, 30 responded to the fractal objects, and 14 (47%) reversed their value biases for the objects between scene A and B. 6 neurons responded to the scenes, but only 1 of them (17%) showed scene-selective response. Among 30 INs, 22 responded to the scenes, and 9 (40%) showed scene-selective responses. 29 neurons responded to the objects, but only 2 of them (7%) reversed their responses to the objects between scene A and B. These results suggest that INs encode the scene-context information, while MSNs encode the value of the objects depending on the scene-context. Importantly, the value-coding of MSNs was stable in each scene, which however was reversed flexibly across the scenes, possibly owing to the inputs from INs. In our daily life, the object values often change in different environments and we can choose different objects accordingly. The mechanisms that we found may support the monkey's flexible switching based on stable long-term experiences of various environments.

**Disclosures: J. Kunimatsu:** None. **O. Hikosaka:** None.

**Poster**

**511. Striatal Circuits in Behavior**

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**Program#/Poster#:** 511.07/PP26

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Post-training intra-dorsolateral striatum infusion of corticosterone enhances consolidation of habit memory

**Authors: *R. RESSLER**, M. G. PACKARD
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**Abstract:** Previous research suggests that stress hormones have a profound influence on several brain structures involved in learning and memory. From a multiple memory systems perspective, exposure to stress has been demonstrated to enhance habit memory mediated by the dorsolateral striatum (DLS) while typically impairing cognitive memory mediated by the hippocampus. One interpretation of stress effects on multiple memory systems is that impairment of hippocampus-dependent memory essentially "unmasks" DLS-dependent memory, leading to a stress-induced bias towards the use of habit memory. Alternatively, recent evidence suggests that the stress hormone corticosterone may act directly within the DLS to enhance consolidation of habit memory. The present experiment further examined the effects of post-training intra-DLS administration of corticosterone on consolidation of habit memory. Adult male Long-Evans rats were trained for five days in a DLS-dependent "response" learning version of a water plus maze task in which they began from different starting positions (North/South) and were required to make a consistently reinforced egocentric body turn response at the maze choice point in order to mount an escape platform. Immediately following maze training on days 1 and 2 animals

received intra-DLS infusion of either corticosterone (10 or 20ng) or vehicle. Post-training administration of corticosterone (20 ng) enhanced memory consolidation and subsequent acquisition of response learning in the plus-maze. The findings are consistent with previous evidence indicating that corticosterone can act directly within the DLS to enhance habit memory consolidation, and suggest that the stress-induced bias towards the use of DLS-dependent habit memory may not only reflect a relative impairment of hippocampus-dependent memory. The results are also consistent with the hypothesis that stress hormones may in part act directly within the DLS to influence the development and expression of maladaptive habitual behaviors observed in various human psychopathologies.

**Disclosures: R. Ressler:** None. **M.G. Packard:** None.

**Poster**

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**Title:** Decreased density of central dopamine type 2 receptors and cognitive impairments in high-sucrose diet-treated rats

**Authors: *D. E. GARCIA-DIAZ**, V. N. HERNANDEZ-SERRATOS, E. M. ACEVES-RODRIGUEZ, E. MARTINEZ-ALONSO, I. ARENAS, H. CASTRO, K. BERMEO
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**Abstract:** Chronic low-grade brain inflammation is closely associated with metabolic disorders and cognitive impairments. These impairments have been suggested to be preceded by derangements in neurotransmitter receptor-dependent signaling pathways. The purpose of this work was to explore whether high sucrose diet-treated animals (HSD) undergo changes in central neurotransmitter receptors and disorganized behavioral tasks. By using radiotracers and positron emission tomography we studied the distribution and density of the membrane protein vesicular monoamine transporter 2 (VMAT2) and dopamine type 2 receptors (D2R) in HSD-treated Wistar rats. D2R are mainly expressed in striatum body (SB). This structure plays a major role in processing and integrating motor signals, also acquisition of motor habits and execution of motor programs critically regulated by dopamine. VMAT2 and D2R were quantified by $C^{11}$-

dihydrotetrabenazine ([$^{11}$C]DTBZ) and [$^{11}$C] Raclopride ([$^{11}$C]RAC), respectively. We found a decreased density of membrane D2R at 30 weeks of HSD treatment in SB (n=5), however, no changes were imaging visible at 15 weeks (n=5). Conversely, VMAT2 increased its density in the same structure after 15 weeks of treatment (n=6), suggesting a homeostatic mechanism preventing loses of membrane receptors. Accordingly, the rotarod test, a standardized behavioral task, confirmed altered motor learning. These results support alterations in behavior and cognition associated with metabolic derangements. These alterations are likely mediated by chronic low-grade inflammation that underlies the cognitive regions of the brain.

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**Poster**

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**Topic:** H.01. Animal Cognition and Behavior

**Title:** Monitoring of corticostriatal synaptic plasticity with an implantable microbiosensor device to understand cognitive performance in neurodegenerative diseases

**Authors: *N. MOORE**[1], C. A. CORDEIRO[2], L. KUHL[2], J. H. A. FOLGERING[2], T. CREMERS[2]
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**Abstract:** The corticostriatal pathway is characterized by a large convergence of cortical neurons into the striatum, and plays a crucial role in motor-skill learning and cognitive performance. This pathway is thought to be involved to modulate striatal synaptic plasticity. Aberrant corticostriatal plasticity has been related to levodopa-induced dyskinesia, a common pathology amongst Parkinson patients. The long lasting, activity dependent changes induced by synaptic plasticity are thought to mediate the ability of the brain to translate experiences into memories. It has been hypothesized that these events could represent the cellular model underlying learning and memory. Depending on the nature of the synaptic modifications, synaptic plasticity can be classified as long-term potentiation (LTP) and long-term depression (LTD).
Although the cellular mechanisms underlying corticostriatal synaptic plasticity are not fully understood, evidence suggests that glutamate receptors (mGlu) are involved in these processes. Synaptic plasticity can be monitored *in vivo* by tracking changes in field Excitatory Post Synaptic Potential (fEPSP) in response to specific stimuli. Fast changes in extracellular glutamate can be monitored by using new developed biosensors with high temporal and spatial resolution (W-Au needle-type microelectrodes).

Glutamate microbiosensors were combined with a monopolar recording electrode (W, 50 µm Ø) and a microinjector and assembled as an implantable microbiosensor device (*i*MBD). To monitor simultaneously synaptic plasticity and glutamate release *in vivo*, the *i*MBDs were placed in the dorsal striatum of anesthetized rats. Additionally, to induce fEPSPs, bipolar stimulation electrodes were placed in the motor cortex (M1). Synaptic plasticity was evoked by applying a high frequency stimulation (HFS) protocol.
Additionally, due to the unprecedented time resolution of our *i*MBD, we identified, following cortical stimulation, a biphasic change in striatal glutamate levels. After HFS, we observed, an immediate (≤5s) increase in glutamate (up to 200 % of basal levels) followed by a fast, but transient decrease. Moreover, we found a long-lasting increase (≥ 90 min post HFS) in glutamate levels in the striatum.
The results obtained using our novel *i*MBD may be the first step to a better understanding of the role of glutamate in synaptic plasticity. Eventually, it may lead to the development of new therapeutic targets for neurodegenerative diseases characterized by aberrant or abnormal synaptic plasticity.

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**Poster**

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**Program#/Poster#:** 511.10/PP29

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Behavioral states determine the effect of dopamine-receptor modulation on oscillatory activity in the rat ventral striatum

**Authors: *P. SCHOENENBERGER**, M. BAINIER, R. LÜTOLF, P. GARCES, O. FAJARDO, J. F. HIPP, R. L. REDONDO
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**Abstract:** The ventral striatum (VS) is a key node in the brain circuitry controlling motivation, decision making, sociability, and reward processing. In humans, dysfunction of striatal activity is associated with a variety of diseases, such as depression, addiction, and schizophrenia (SZ). Excitatory input from cortical and limbic structures, as well as prominent dopaminergic signals, converge in the VS. There, medium spiny neurons (MSNs) are inhibitory projection neurons classically divided into D1 receptor (D1R)-expressing- and D2 receptor (D2R)-expressing neurons. Alterations in dopamine (DA)-mediated modulation of VS MSN activity is thought to contribute to disease symptoms such as lack of motivation in SZ, or drug seeking in addiction. Specific D1 vs D2 modulation has been pursued as a therapeutic approach to rebalance basal

ganglia function. To better understand those potential therapies, we studied the effect of systemic application of D1- or D2-specific receptor modulators on striatal local field potentials (LFPs) and EEG in freely moving rats. As reported previously, VS activity spontaneously alternates between 50 Hz- and 80-Hz gamma bursts. Interestingly, both pharmacological activation and blockade of D1Rs with SKF81279 or SCH39166, respectively, led to strong increases in gamma activity, but in non-overlapping frequency bands. In addition, some of these effects were limited to particular behavioral states. Specifically, D1R activation resulted in an increase in 80 Hz-gamma during both exploration and rest, whereas SCH39166 increased 50 Hz-gamma power, but this increase was observed only during rest periods. Activation of D2Rs by quinpirole led to an increase in 50 Hz-gamma power and a concomitant reduction in the mean frequency in several oscillatory bands. This is in stark contrast to the effect of D2R blockade by raclopride, a widely-used antipsychotic, on VS oscillations. Complementary EEG recordings provided a global measure of DA receptor-modulator action and we found consistent modulation of EEG activity under several of the conditions tested. These EEG signals have a high translational potential and the knowledge on EEG signatures of different DA receptor modulators may serve as a reference to develop novel therapeutic agents. In summary, we show that modulation of D1R and D2R activity reveals distinct signatures in VS oscillatory activity, which may provide a framework for the development of novel therapeutics seeking to normalize VS pathways. Importantly, the effect of different modulators is determined by behavioral states. Understanding the mode of action of candidate therapies needs to take this variable into account.

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**Poster**

**511. Striatal Circuits in Behavior**

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Brain/MINDS, AMED to MT

**Title:** Organization of multisynaptic inputs from the basal ganglia and cerebellum to the anterior and posterior cingulate cortical areas in common marmosets: Retrograde transneuronal double labeling with fluorescent rabies viral vectors

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**Abstract:** The basal ganglia and cerebellum contribute to various aspects of motor functions. These motor centers constitute multisynaptic loop circuits with the cerebral cortex. The anterior (ACC), but not posterior (PCC), cingulate cortex is considered to give rise to the limbic loop through the ventral striatum, ventral pallidum, and mediodorsal nucleus of the thalamus. However, it has previously been reported in macaque monkeys that the cingulate cortex, including the ACC, sends fibers directly to the dorsal striatum, as well as to the ventral striatum. In addition, the neuronal connectivity between the cingulate cortex and the cerebellum remains to be clarified. Therefore, the present study was undertaken to investigate how the cingulate cortex connects multisynaptically with the basal ganglia and cerebellum by means of retrograde transneuronal double labeling with fluorescent rabies viral vectors; the ACC and PCC in common marmosets were injected separately with the viral vectors expressing GFP and RFP. After the vector injections, the animals were allowed to survive for about 48 and 65 hours to achieve the second- and third-order neuron labeling, respectively. With the 48-hour survival period, the distribution patterns of labeled neurons in the basal ganglia (i.e., internal segment of the globus pallidus and substantia nigra pars reticulata) varied in the ACC vs. PCC injection cases. In the deep cerebellar nuclei, all of the medial, interposed and lateral nuclei contained neuronal labeling after the ACC injection, while the PCC injection produced neuronal labeling in the interposed and lateral nuclei. Such a discrepancy of labeled neuron distribution also occurred with the 65-hour survival period. In the basal ganglia, the labeled neurons were located not only in the ventral striatum, but also distinctly in the putamen and caudate nucleus after the ACC or PCC injection, respectively. Likewise, Purkinje cell labeling within the cerebellar cortex was distributed in both the vermis and the hemisphere after the ACC injection, but in the hemisphere alone after the PCC injection. The present results indicate that multisynaptic inputs from the basal ganglia and cerebellum to the ACC vs. PCC are organized in a differential fashion.

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**Poster**

**511. Striatal Circuits in Behavior**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 511.12/QQ2

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NEI Intramural

**Title:** Optogenetic modulation of saccade-controlling circuits in the monkey basal ganglia

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**Abstract:** Optogenetics enables to control a specific neuronal pathway. However, few studies have used this technique to study the neuronal circuits in non-human primates (Inoue et al. Nat Com 2015). We applied pathway-selective optogenetics to investigate the oculomotor mechanism of the basal ganglia circuits.
We injected a viral vector (AAV2-CMV-ChR2-EYFP) into the tail part of the caudate nucleus (CDt) of a macaque monkey to perform optogenetics experiments (see below). Histological examinations (done later) showed that ChR2 was expressed in cell bodies in CDt and axon terminals of CDt neurons in the caudal-dorsal-lateral part of the substantia nigra pars reticulata (cdlSNr) and the caudal-ventral part of the globus pallidus externus (cvGPe).
As the first step of optogenetics experiment, we examined the effect of optical stimulation on single neuron activity in CDt using optrodes. Most GABAergic interneurons (INs) (17/19, 89%) were activated tonically. In contrast, medium spiny neurons (MSNs) were tonically inhibited, some of which (2/19, 11%) showed a brief initial activation. These data suggest that INs, which are tonically active, can continue to suppress the output of CDt. Next, we examined whether the optical stimulation of the CDt axon terminals affected postsynaptic neurons in cdlSNr and cvGPe. Many visual neurons (27/43, 63% in cdlSNr; 30/49, 61% in cvGPe) were inhibited, indicating that they received direct inhibitory inputs from CDt. Some of them (11/27, 41% in cdlSNr; 15/30; 50% in cvGPe) showed stable value coding, suggesting that stable value signals originated from CDt. Interestingly, these inhibitory responses were short (5-20 ms), sometimes followed by excitatory responses. In contrast, few non-visual neurons (5/17, 29% in cdlSNr; 1/23, 4% in cvGPe) were affected by the optical stimulation, suggesting that CDt sends mainly visual information to cdlSNr and cvGPe.
Finally, we examined the behavioral effects while the monkey was freely viewing multiple objects. The optical stimulation in cdlSNr facilitated contralateral saccades and suppressed ipsilateral saccades. This effect provides evidence for the facilitatory effect of the direct pathway. More specifically, optical stimulation in cdlSNr selectively activated the inhibitory input from CDt to cdlSNr neurons (shown above), which led to a disinhibition of SC neurons and the facilitation of contralateral saccades. The present study is an important step for investigating the mechanism and function of neuronal circuits in the primate basal ganglia.

**Disclosures: H. Amita:** None. **H.F. Kim:** None. **K. Inoue:** None. **M. Takada:** None. **O. Hikosaka:** None.

**Poster**

**511. Striatal Circuits in Behavior**

**Location:** Halls A-C

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**Topic:** H.01. Animal Cognition and Behavior

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**Title:** The cortico-striatal adenosine $a_{2a}$ receptors control spatial working memory in mice and monkeys

**Authors: *Z. LI**[1], X. CHEN[1], T. WANG[2], F. LI[1], L. CHEN[1], F. YUE[2,3], P. CHAN[2,3], J.-F. CHEN[1,4]
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**Abstract:** Spatial working memory (SWM) is fundamental to cognition by caching behaviorally relevant cues on a timescale of seconds. The medial prefrontal cortex (mPFC) is specially wired to support WM with its persistent neuronal activity in the absence of stimulation while the striatum is postulated to gate WM representations. The adenosine $A_{2A}$ receptor ($A_{2A}R$) is expressed in the cortico-striatal pathway with highly enrichment in the striatopallidal neurons where it integrates dopamine and glutamate signaling to modulate cognition. Our recent genetic and optogenetic studies have implicated the cortico-striatal $A_{2A}R$ in modulation of WM, but the circuit mechanism underlying the cortico-striatal $A_{2A}R$ control of WM is not clear and the therapeutic potential of $A_{2A}R$ antagonists has not been tested in non-human primates. By coupling Cre-loxP-mediated focal $A_{2A}R$ knockdown (KD) with a delayed non-match-to-place (DNMTP) working memory task, we demonstrated the respective effects of focal knockdown of $A_{2A}Rs$ in the dorsomedial striatum (DMS) and mPFC on SWM and also evaluated the effect of systemic administration of KW6002 on DNMTP performance. $A_{2A}R$ signaling in mPFC and DMS exerted opposite modulations of SWM, with focal KD of DMS $A_{2A}Rs$ apparently enhanced while focal KD of mPFC $A_{2A}Rs$ impaired DNMTP performance. Moreover, the $A_{2A}R$ antagonist

KW6002 produced the similar effect of the DMS $A_{2A}$R KD, indicating that KW6002 mainly and predominately acts at the striatopallidal $A_{2A}$Rs in DMS to control SWM. Lastly, as the $A_{2A}$R antagonist is currently evaluated for its motor benefit in Parkinson's disease (PD) patients, we also evaluated the effect of KW6002 on delayed match-to-sample/place (DMTS/DMTP) task in normal and dopamine-depleted Cynomolgus monkeys to explore the potential pro-cognitive benefit in PD. We demonstrated that KW6002 treatment improved SWM performance in DMTS and DMTP tasks of normal and MPTP-treated Cynomolgus monkeys. Together, these findings suggest that the $A_{2A}$R in striatopallidal and mPFC neurons exert distinctive control of SWM to achieve cognitive stability and flexibility. Furthermore, the pro-cognitive effect of $A_{2A}$R antagonists in non-human primate provides the preclinical data to translate $A_{2A}$R antagonists for improving cognitive impairments in PD.

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**Poster**

**511. Striatal Circuits in Behavior**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 511.14/QQ4

**Topic:** H.01. Animal Cognition and Behavior

**Support:** National Institute on Aging's Post-Doctoral Funding Opportunity award

**Title:** Striosome roles in anxiety and choice behavior

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**Abstract:** Parkinson's disease (PD) non-motor symptoms include elevated anxiety and altered decision-making. Altered activity in striosome neurons might support this non-motor phenotype, given that striosomes are an intersection for prefrontal, limbic, and reward circuitry, and have been recently implicated in cost-benefit decision-making. Moreover, striosomes are enriched in the PD-linked *Lrrk2* gene. Using chemogenetics to modulate striosome activity in male and female mice, we identify striosome-dependent behaviors. In particular, we find that reduced striosome activity reduces risky reward-seeking, and alters performance on the elevated zero maze. No sex difference is detected. *In vivo* calcium imaging will be used to study striosome dynamics accompanying the same behaviors in mice. Preliminary results using this method demonstrate a selection of striosome neurons activated by a cue signaling the start of operant trials. Completed findings in wild type mice will form a basis for future comparison to mice carrying PD-relevant Lrrk2 mutations.

**Disclosures:** **S.L. Hawes:** None. **G. Barbera:** None. **B. Liang:** None. **D. Lin:** None. **H. Cai:** None.

**Poster**

**511. Striatal Circuits in Behavior**

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**Program#/Poster#:** 511.15/QQ5

**Topic:** H.01. Animal Cognition and Behavior

**Support:** KAKENHI (no. 17H06036) from the MEXT

**Title:** Chunk learning from complex sequences by mutually supervising recurrent neural networks

**Authors:** ***T. ASABUKI**, T. FUKAI
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**Abstract:** Detecting meaningful clusters (chunks) from sequences is a critical element of high-order brain functions such as language acquisition and motor sequence learning. Moreover, chunk learning enables the brain to construct compact representations of complex sequence information, and hence supports the brain's ability of modeling the external world. Chunking is composed of segmentation and concatenation, and several computational studies have modeled these processes. Yet, unsupervised learning of chunks from complex sequences is a challenge for neural network models. Here, we extend the reservoir computing to a novel framework of chunk learning. The proposed model are composed of two recurrent networks that mutually supervise their chunk learning. While each reservoir undergoes supervised learning, the entire network is trained in an unsupervised manner. We explore the conditions required for successful learning and found that noise plays an active role in the proposed chunk learning. Interestingly, when the chunk learning is successful, readout neurons from the reservoirs display a characteristic activity that piles up during the exposure to a specific chunk and rapidly decays outside of it. Some striatal neurons called "STOP cells" indeed show such an activity pattern when a particular motor sequence is repeatedly learned. Thus, our model gives a novel insight into the biological mechanisms of chunk learning.

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**Poster**

**511. Striatal Circuits in Behavior**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** R01 R01MH086629

NARSAD

FSU College of Medicine

FSU Center for Brain Repair

**Title:** Selective loss of dopamine D2 receptors in GABAergic interneurons modifies cerebral cortical architecture and motor behaviors

**Authors: *G. S. LEE**[1], D. L. GRAHAM[1], L. R. ANDERSON[1], T. S. TRAMMELL[1], M. RUBINSTEIN[2], G. D. STANWOOD[1]
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**Abstract:** Dopamine D2 receptors (D2Rs) modulate a wide range of behavioral and cognitive functions including movement, cognition, and reward. They also play fundamental roles in neurodevelopment, including effects on forebrain differentiation, cerebral cortical interneuron number, and behavioral function. Moreover, disrupted D2R expression and/or signaling contributes to neuropsychiatric disorders including depression, schizophrenia, and attention deficit disorders. To further understand the role of the D2R in frontal cortical interneuron development, we generated a conditional D2R knockout mouse model. D2R was deleted from frontal cortical GABAergic neurons using Nkx2.1-Cre mice to target GABAergic interneuron progenitors from the medial ganglionic eminence. Conditional Nkx2.1.D2RKO mice exhibited no differences in tests of spontaneous locomotor activity, anxiety, depression-related behaviors or working and spatial memory. Nkx2.1.D2RKO mice exhibited greater latencies to fall during a rotarod task, suggesting enhanced motor coordination. Nkx2.1.D2RKO mice exhibited reduced locomotor activity induced by MK-801, suggesting that NMDA receptor antagonist-induced locomotion requires D2R expression in cortical GABAergic neurons. At the cellular level, no significant changes in the number of GAD67+ or parvalbumin+ neurons were observed in the anterior cingulate cortex in adult mice. However, Nkx2.1.D2RKO mice showed a decrease in numbers of parvalbumin+ neurons surrounded by glycan-binding *Wisteria floribunda agglutinin*. This suggests that loss of D2R leads to decreased perineuronal nets around parvalbumin+

neurons which may, in turn, contribute to reduced synaptic stability. Ongoing studies to examine forebrain circuitry and gene expression patterns are underway to identify the developmental, cellular, and behavioral roles of D2R within GABAergic neurons of the telencephalon, and the mechanisms by which D2R dysfunction contributes to the development and pathophysiology of brain disorders.

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**Poster**

**511. Striatal Circuits in Behavior**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 511.17/QQ7

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIAAA IRP

**Title:** Dorsolateral striatal modulation of choice learning and flexibility

**Authors: *A. G. LIEBERMAN**[1], H. C. BERGSTROM[2], C. GRAYBEAL[1], A. M. LIPKIN[3], A. HOLMES[1]
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**Abstract:** Cognitive flexibility, the ability to rapidly alter behavior in response to changing circumstances, is impaired in many psychiatric and neurological disorders, yet the neural substrates of cognitive flexibility remain understudied. Reversal learning is an assay of cognitive flexibility that measures the ability to suppress a habitual response while updating to altered stimulus-outcome contingencies. Current theories implicate the dorsomedial striatum in goal-directed learning that is quickly acquired and highly sensitive to changes in outcome, while the dorsolateral striatum (DLS) drives the subsequent stimulus-bound or habitual performance of actions. However, recent work provides evidence that the mouse DLS is active from the earliest stages of learning a discrimination touchscreen task. Building on these findings, we examined whether the DLS may also be recruited in tasks demanding choice flexibility. To examine whether one DLS output pathway is preferentially recruited during early reversal, we trained naïve C57BL/6J mice on the discrimination task or a subsequent reversal task – in which the previously rewarded stimulus was now rewarded and the unrewarded stimulus was no longer rewarded. Mice were sacrificed after either early discrimination or early reversal training to determine differential patterns of activation in the DLS, via *in situ* hybridization of the immediate-early gene, Arc. Activation was further parsed out as a function of whether it occurred in direct output or indirect output pathway DLS neurons, via *in situ* hybridization of

*Drd1* or *Drd2*, respectively. Next, to interrogate the causal contribution of the direct and indirect pathways on reversal learning, we optogenetically silenced either the direct or indirect pathway (by targeting an AAV carrying the inhibitory opsin, ArchT, in *Drd1*-Cre or *Adora2a*-Cre mice, respectively) as mice made choices during reversal. Results provide further evidence that the DLS may have a previously underappreciated role in modulating cognitive flexibility, with implications for understanding how DLS dysfunction might contribute to disorders characterized by inflexible behavior.

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**Poster**

**511. Striatal Circuits in Behavior**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 511.18/QQ8

**Topic:** G.07. Other Psychiatric Disorders

**Title:** Lumateperone (ITI-007) is a postsynaptic D2 receptor antagonist

**Authors: *J. P. HENDRICK**, L. ZHANG
Intra-Cellular Therapies Inc, New York, NY

**Abstract:** *Rationale* ITI-007 (lumateperone) is a new molecular entity with a first-in-class pharmacological profile. ITI-007 is a high affinity serotonin 5-$HT_{2A}$ receptor antagonist with lower but clinically relevant affinity for other targets, including dopamine $D_1$ and $D_2$ receptors and serotonin transporters. ITI-007 also indirectly modulates both NMDA and AMPA glutamate neurotransmission in the prefrontal cortex via D1 receptor and SERT interactions. ITI-007 lacks significant activity at other receptors (e.g., $H_1$, muscarinic, 5-$HT_{2C}$) that may cause unwanted and deleterious effects. In previous studies in vivo, we have shown that ITI-007 is both a pre-synaptic partial agonist (no effect on dopamine metabolism and protein phosphorylation profile consistent with presynaptic partial agonism in the striatum) and post-synaptic antagonist (protein phosphorylation consistent with postsynaptic antagonist activity) (Li et al., 2014, J Med Chem 27:2670; Snyder et al., 2014, Psychopharm, 232:605). We now have further explored the unique interactions of ITI-007 with dopamine receptors *in vitro* to assess its functional D2 activity in systems mimicking a postsynaptic cell. In similar systems, other antipsychotic drugs with partial D2 agonist activity demonstrate partial agonism presynaptically *in vivo*, and postsynaptically as revealed *in vitro* in cells (Burris et al., 2002, JPET, 302:381; Maeda et al., 2014, JPET, 350:589).
*Objectives*: To characterize the D2 functional activity of lumateperone under conditions sensitive to D2 partial agonists in a system mimicking a postsynaptic cell.
*Results*: In contrast to three known postsynaptic partial agonists, bifeprunox, aripiprazole, and brexpiprazole, lumateperone displayed no demonstrable postsynaptic partial agonist activity,

behaving as a D2 antagonist in this system.
*Conclusion*: As noted previously, lumateperone acts in vivo as a presynaptic partial agonist and a postsynaptic antagonist. Data presented here confirm our previous in vivo findings that lumateperone functions as a postsynaptic antagonist. The ability of ITI-007 to act both as a pre-synaptic partial agonist and post-synaptic antagonist is unique and not shared by other antipsychotic drugs.

**Disclosures: J.P. Hendrick:** A. Employment/Salary (full or part-time):; Intra-Cellular Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intra-Cellular Therapies, Inc. **L. Zhang:** A. Employment/Salary (full or part-time):; Intra-Cellular Therapies, Inc..

**Poster**

**511. Striatal Circuits in Behavior**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 511.19/QQ9

**Topic:** H.01. Animal Cognition and Behavior

**Support:** BBSRC Grant BB/M009440/1

**Title:** GluA1 AMPA receptor subunit deletion abolishes reinforcement rate learning in mice

**Authors: *J. M. AUSTEN**[1], R. SPRENGEL[2], D. J. SANDERSON[1]
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**Abstract:** Conditioning occurs more readily with cues of short duration than of long duration. One possible explanation for this phenomenon is that the long duration cues undergo more short-term habituation than the short cues, and this results in poorer learning when reinforcement occurs. GluA1 AMPA receptor subunit deletion in mice reduces short-term habituation; therefore, if the short-term habituation account of the cue duration effect has merit, mice lacking the GluA1 subunit should show a reduced cue duration effect. Mice received appetitive Pavlovian conditioning with a 10 s cue and a 40 s cue. Control mice showed greater learning with the 10 s cue than the 40 s cue; however, as predicted, GluA1 deletion abolished this cue duration effect. Subsequent experiments demonstrated that, rather than being driven by short-term habituation, the cue duration effect seen in control mice primarily reflected sensitivity to the rate of reinforcement across cumulative exposure to the cues (e.g., a 40 s cue has a lower rate of reinforcement than a 10 s cue). The cue duration effect was not seen in GluA1 knockout mice as they were sensitive only to the number of times that a cue was paired with reinforcement, regardless of the reinforcement rate of that cue. These results suggest that, in addition to its previously demonstrated role in short-term habituation, GluA1 is also responsible for weighting

numeric, trial-based information by temporal information in order for animals to achieve rate-based learning. Associative accounts of learning can explain rate-sensitivity in terms of the balance between increments and decrements in associative strength over cumulative exposure to cues. Learning in GluA1 knockout mice may be explained in terms of a failure to reduce associative strength during periods of nonreinforced exposure. This leads to the hypothesis that GluA1 is necessary for changes in learning that occur due to negative prediction error.

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**Poster**

**511. Striatal Circuits in Behavior**

**Location:** Halls A-C

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** BBSRC Grant BB/M009440/1

**Title:** GluA1 AMPA receptor subunit deletion impairs blocking of flavour preference learning

**Authors:** ***J. A. STRICKLAND**[1], J. M. AUSTEN[1], R. SPRENGEL[2], D. J. SANDERSON[1]
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**Abstract:** The GluA1 AMPA receptor subunit plays an important role in learning and memory, with GluA1 knockout mice showing impaired short-term habituation to recently experienced stimuli. An account of GluA1 proposed by Sanderson et al. (2009) presumes that GluA1 is not necessary for associative retrieval and, by extension, prediction error. As yet, however, there have been no direct tests of this hypothesis. We tested this prediction by assessing blocking of flavour preference learning in GluA1 knockout mice. In stage 1 mice drank flavour A paired with 32% sucrose and flavour B paired with 4% sucrose. In stage 2 mice drank compounds of flavours A and X, and B and Y. Each compound was paired with 32% sucrose. In the test session mice were allowed to drink flavours X and Y. Control mice showed a preference for flavour Y indicating that flavour A had blocked learning of flavour X. Contrary to the original hypothesis, GluA1 knockout mice failed to show blocking of learning. A subsequent test phase demonstrated that the lack of blocking in knockout mice was not due to a failure to learn about the blocking flavour. While these results suggest that the role of GluA1 may extend to cue competition effects, it is not clear to what extent performance in the current experiment is influenced by within-compound associations and to what degree GluA1 deletion affects these associations.

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**Poster**

**511. Striatal Circuits in Behavior**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** BBSRC grant BB/M009440/1

**Title:** The GluA1 subunit of the AMPA receptor is necessary for rate-sensitive learning but not learning that is dependent on the number of reinforcements

**Authors: *D. J. SANDERSON**[1], R. SPRENGEL[2], J. AUSTEN[1]
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**Abstract:** We have found that appetitive Pavlovian conditioning in mice is determined by the rate of reinforcement. Mice that lack the GluA1 subunit of the AMPA receptor fail to show rate-sensitive learning. In the previous experiments the rate of reinforcement was manipulated by comparing cues with different durations (10 s versus 40 s) and rate was equated by confounding the variables of cue duration and probability of reinforcement per trial (e.g., a 10 s cue reinforced on 25% of trials compared to a 40 s cue reinforced on 100% of trials). It is possible that GluA1 is necessary for rate learning when cue duration is manipulated because of its role in short-term habituation. Therefore, in order to test whether GluA1 is necessary for rate learning regardless of cue duration, mice were trained with two cues of the same duration that were reinforced at different rates. One cue was reinforced on every trial and the other was reinforced on 25% of trials. The partially reinforced cue was presented four times more often than the continuously reinforced cue such that the number of reinforcements was equated between the cues. Normal mice were sensitive to reinforcement rate and showed better learning with the continuously reinforced cue than the partially reinforced cue. GluA1 knockout mice, however, showed equal learning with the two cues. In a second experiment mice were trained with two cues of the same duration that were reinforced at the same rate, but one cue was presented four times more often than the other such that the cues differed in the number of times that they were paired with reinforcement. Both normal and GluA1 knockout mice showed superior learning with the cue that received a higher number of reinforcements. These results demonstrate that GluA1 is necessary for reinforcement rate learning regardless of whether rate is manipulated by cue duration or probability of reinforcement per trial. The fact that in the absence of GluA1 learning switches to being dependent on the number of reinforcements suggests that GluA1 plays a crucial role in the time-dependent aspects of learning that result in sensitivity to rate information.

**Disclosures: D.J. Sanderson:** None. **R. Sprengel:** None. **J. Austen:** None.

**Poster**

**512. Reward: Motivational Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 512.01/QQ12

**Topic:** G.02. Motivation

**Support:** NIH Grant DA035943

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NIH Grant DA042895

**Title:** Encoding of conditioned motivation by midbrain dopamine neurons

**Authors: *B. T. SAUNDERS**[1], J. M. RICHARD[1], P. H. JANAK[2]
[1]Dept. of Psychological and Brain Sci., [2]Johns Hopkins Univ., Baltimore, MD

**Abstract:** Conditioned motivational states evoked by rewards and associated stimuli (conditioned stimuli, CSs) are essential for adaptive reward seeking, but they also contribute to a variety of psychiatric disorders, such as addiction. Despite this, we lack a circuit-level understanding of how the brain creates motivation under normal and pathological conditions. Dopamine neurons originating from the ventral tegmental area (VTA) and substantia nigra (SN) have received considerable attention for their role in reward-related processes, but it remains unclear what information is signaled by CS-evoked neural activity within these systems, and how that maps on to conditioned behaviors. To explore this issue, we used fiber photometry to measure activity of dopamine neurons in TH-cre rats expressing GCaMP6. We found that through Pavlovian conditioning, sensory cues paired with optogenetic activation of VTA dopamine neurons become CSs that evoke dopamine neuron activity in the VTA, and elicit conditioned behavioral responses. Furthermore, the magnitude of the cue-evoked dopamine signal predicted the vigor of cue-evoked conditioned behavior. This suggests that rather than simply signaling the learned predictive value of a Pavlovian CS, VTA dopamine neurons encode its incentive motivational value to actually drive actions. We are currently investigating if cue-evoked dopamine neuron signals vary as a function of the sensory modality of the predicted outcome (i.e., optogenetic brain stimulation versus delivery of an external, consumable reward) and across dopamine neuron subpopulations (e.g., VTA versus SN). The goal of these studies is to better understand how phasic dopamine neuron activity contributes to cue-evoked motivational states that drive reward-specific behaviors.

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**Poster**

**512. Reward: Motivational Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 512.02/QQ13

**Topic:** G.02. Motivation

**Support:** NIH Grant R01 DA035943

**Title:** Extended experience does not alter the role of dopamine in the nucleus accumbens core, nor recruit dorsal lateral striatum, to facilitate Pavlovian cue approach

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**Abstract:** The attribution of incentive salience to reward-paired cues is dependent on dopamine release in the nucleus accumbens core. These dopamine signals conform to traditional reward-prediction error signals and have been shown to diminish with time following extended training. Here we examined if the diminishing dopamine signal in the nucleus accumbens core has functional implications for the expression of sign-tracking, a Pavlovian conditioned response indicative of the attribution of incentive salience to reward-paired cues. Food-restricted rats were trained in a Pavlovian paradigm in which an insertion of a lever predicted delivery of food reward in a nearby food cup. After 7 or 14 training sessions, rats received in separate sessions infusions of saline, the dopamine antagonist, flupenthixol, or a mixture of the GABA agonists, baclofen and muscimol, into the nucleus accumbens core or the dorsal lateral striatum. Dopamine antagonism within the nucleus accumbens core attenuated sign-tracking, whereas reversible inactivation did not affect sign-tracking but increased non-specific food cup checking behaviors. Neither drug in the dorsal lateral striatum affected sign-tracking behavior. Critically, extended training did not alter these effects. Though extended experience with a Pavlovian incentive cue is reported to reduce cue-evoked dopamine in the nucleus accumbens core, our results suggest this does not alter the function of dopamine in this region to promote Pavlovian cue approach nor result in the recruitment of dorsal lateral striatal systems for this behavior. These data support the notion that dopamine within the mesoaccumbal system, but not the nigrostriatal system, contributes critically to incentive motivational processes independent of the length of training. Future investigations are exploring ways in which cues can proactively invigorate or dampen future reward-seeking driven by ambiguously predictive stimuli.

**Disclosures: K.M. Fraser:** None. **P.H. Janak:** None.

**Poster**

**512. Reward: Motivational Mechanisms**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** G.02. Motivation

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**Title:** Lateral hypothalamic GABAergic projections to VTA mediate consummatory responses toward fat-enriched foods

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**Abstract:** The lateral hypothalamus (LH) exhibits a vast heterogeneity of cell types and connectivity. Until recently, this complexity prevented the study of specific cell populations and their involvement in motivated behaviors. Novel optogenetic approaches have shown that a GABAergic LH neuronal subpopulation is involved in feeding and reward. Nonetheless, the neurocircuitry involved remains unknown. An interesting downstream candidate is the ventral tegmental area (VTA), a region largely implicated in reward-related behaviors. In the present study, we investigated if the GABAergic LH to VTA circuit was involved in the expression of consummatory behaviors by using a combination of optogenetic and behavioral techniques in male VGaT-Ires-Cre mice. We found that VTA photoinhibition of GABAergic LH terminals decreased the operant responses and amount of fat-enriched pellets earned when applied during the entire experimental session of a fixed ratio 5 (FR5) food-reinforced task, as well as of a progressive ratio 3 (PR3). Interestingly, the same results were observed when the photoinhibition was restricted to the consumption phase of FR5 and PR3. The inhibition was ineffective when administered to control animals. Next, we conducted free-feeding experiments and studied if the inhibition of the GABAergic LH terminals in the VTA modified consummatory responses depending on the type of food presented. We observed a decrease in the amount eaten and an increase in the latency to initiate eating when mice were presented with fat-enriched pellets. On the contrary, the inhibition was ineffective when mice were presented with either standard chow or grain-based pellets. Our results demonstrate that inhibition of GABAergic fibers originating in the LH and projecting to the VTA are preferentially implicated in the encoding of consummatory responses for fat-enriched foods. They are consistent with a model in which the LH, given its unique connectivity and neurochemical expression pattern, may convey pertinent homeostatic information to the VTA, which, in turn, and as a key component of the mesocorticolimbic circuitry, can orchestrate goal-directed consummatory behaviors that are critical for survival.

**Disclosures:** **M.F. Barbano:** None. **D.N. Acs:** None. **P.H. Janak:** None.

**Poster**

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**Title:** Ventral pallidal encoding of reward seeking depends on the underlying associative structure

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**Abstract:** Activity in ventral striatopallidal circuitry is thought to be a critical mechanism by which previously neutral cues are able to elicit reward seeking following learning. Recently we have shown that the activity of ventral pallidum (VP) neurons in response to a cue predicting reward availability encodes both the likelihood and latency of subsequent instrumental reward-seeking actions (Richard et al., 2016). Here, we investigated whether VP cue responses would encode and contribute similarly to the vigor of Pavlovian versus instrumental reward seeking behaviors, when these responses consist of superficially similar locomotor response patterns, and are driven by similar levels of reward expectancy. During Pavlovian conditioning, male and female Long Evans rats were trained to associate one auditory cue (the CS+) with delivery of 10% liquid sucrose reward (not contingent on the animal's behavior) and alternative auditory cue (CS-) with no delivery of reward. In the instrumental task, one auditory cue (the discriminative stimulus; DS) signaled availability of the same sucrose reward, if the animal made an entry into the reward port during the cue period; the alternative cue (NS) signaled no reward availability. Rats were trained in one of these tasks until they entered the reward port on >70% of reward cue trials (CS+ or DS), and <30% of control cue trials (CS- or NS), and then were implanted with drivable microwire arrays aimed at VP. We found that, similarly to our previous report, cue elicited activity in ~25% of VP neurons significantly predicts the latency of instrumental reward seeking, even when it consists of a much simpler behavior: entry to a reward port. In contrast, VP encoding of Pavlovian port entry latency did not exceed chance levels. Further, when we

assessed the impact of either VP inactivation with GABA agonists, or dopamine blockade, with the non-selective antagonist flupenthixol, we found that only the latency of reward seeking driven by the DS, but not by the CS+, was affected by these manipulations. These results suggest that VP encoding of latency, as well as the functional contributions of both VP activity and dopamine inputs, are not related to trial-by-trial variation in the value of the expected reward, or to motor invigoration more generally, but to the ability of incentive cues to invigorate reward seeking behaviors upon which reward delivery is contingent.

**Disclosures:** **J.M. Richard:** None. **N. Stout:** None. **D. Acs:** None. **P.H. Janak:** None.

**Poster**

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**Topic:** G.02. Motivation

**Support:** NIH 5T32NS091018-17

NIH R01 DA035943

**Title:** Nucleus accumbens neural activity reflects reward preference and predicts consumption

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**Abstract:** The nucleus accumbens (NAc) has long been implicated in the orchestration of reward seeking and consumption. Despite its demonstrated involvement in the processing of a variety of drug and natural rewards, it is less clear how responses in the NAc differ across these rewards. The study of NAc activity in response to rewards with different properties can help characterize which aspects of reward processing the NAc is involved in. Using in vivo extracellular recording, we measured the responses of NAc single units during the consumption of 10% solutions of sucrose and maltodextrin, two rewards of very similar caloric value and palatability. Male Long Evans rats were trained on a single cue that announced the availability of a reward whose delivery was contingent upon port entry. Sucrose and maltodextrin trials were randomly interspersed throughout the session in order to obscure the identity of the reward until its delivery. Rats' individual licks were recorded using a custom-built lickometer that permitted analysis of consumption behavior and corresponding neural activity. Rats licked a similar amount to both rewards although slightly more during consumption of sucrose. This preference was reflected in NAc neural activity, which was biased toward stronger responses during sucrose consumption than maltodextrin. Analysis of the neural activity in 500ms bins, with a sliding

window of 100ms, revealed the greatest difference in firing across rewards occurred between 0.5s and 2.5s after reward consumption onset, following an initial non-reward-specific spike in activity. Moreover, we found that firing rate during the middle portion of reward consumption predicted the total number of licks on a trial-by-trial basis for a large proportion of the population of neurons. This group of lick-correlated neurons fired more strongly during sucrose consumption than maltodextrin, a potential indication that the difference in firing to the two rewards is in part due to the increased licking for sucrose. These results suggest that NAc neurons may be involved in integrating the palatability of rewards in order to direct reward consumption behavior.

**Disclosures: D.J. Ottenheimer:** None. **J.M. Richard:** None. **P.H. Janak:** None.

**Poster**

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**Topic:** G.02. Motivation

**Support:** NIH R01 DA035943

**Title:** Phasic activation of ventral tegmental but not substantia nigra dopamine neurons promotes model-based pavlovian reward learning

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**Abstract:** Dopamine (DA) neurons in the ventral tegmental area (VTA) signal reward prediction errors (RPEs) and their activation constitutes a teaching signal that promotes learning about the events leading up to reward. DA neurons in the Substantia Nigra (SNc) also encode RPEs but their functional role in error-correction learning is unclear. Moreover the learning strategy engaged by RPEs remains largely unknown. RPEs could promote model-free learning in which animals learn the value of cues and actions independently of the representation of their outcomes, resulting in rigid behavior insensitive to postconditioning changes in outcome value. Alternatively, through model-based learning, RPEs could contribute to the construction of internal models of the task by connecting certain events with their respective outcome, allowing animals to rapidly adjust their behavior following changes in outcome value. Therefore, the purpose of this study was twofold: 1) Assess the contribution of VTA- and SNc-DA neuron activation in Pavlovian reward learning, and 2) When learning was observed as a result of our manipulations, determine the model-free or model-based nature of this learning. Rats were trained in a Pavlovian blocking paradigm, in which learning about a target cue paired with

reward is prevented (or blocked) if this cue is presented simultaneously with another cue that already signals reward. In this situation, the absence of RPE, presumably materialized by the absence of phasic DA responses, is thought to prevent learning about the redundant target cue. Consistent with the idea that VTA-DA neurons encode a RPE teaching signal, we show that optogenetic activation of VTA-DA neurons during expected reward unblocks learning about the target cue. In contrast, optogenetic activation of SNc-DA neurons did not promote Pavlovian learning (learning remained blocked). This is despite the fact that activation of both VTA- and SNc- DA neurons serve as potent reinforcers in self-stimulation procedures. To determine the associative content of the learning promoted by VTA-DA neurons activation, we combined the blocking paradigm with postconditioning devaluation of the outcome (via lithium-induced taste aversion). We found that the expression of VTA-DA dependent learning is affected by outcome devaluation which indicates that the learned association integrates a representation of the outcome, a signature of model-based learning. These findings reveal that activation of VTA- or SNc-DA neurons engages largely dissociable learning processes with VTA-DA neurons capable of participating in complex model-based predictive learning, while the role of SNc-DA neurons is more limited.

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**Poster**

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**Topic:** G.02. Motivation

**Support:** NIH R01 DA035943

AA014925

**Title:** Motivational stake promotes goal-directed behavior

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**Abstract:** Balance between goal-directed and habitual response strategies is necessary for flexible and efficient decision-making. While goal-directed behavior is considered dependent upon Response-Outcome (R-O) associations, habit instead relies on Stimulus-Response (S-R) associations. However, the stimuli that support the S-R association underlying habitual responding in instrumental procedures are poorly defined. To resolve this issue, we designed a discrete-trials procedure, in which rats must wait for lever insertion and complete a sequence of 5

lever presses to obtain a reward (20% sucrose or grain-based pellets). Lever insertion thus constitutes an audio-visual stimulus signaling the availability of the reward. Using sensory-specific satiety-induced devaluation, we found that food-restricted rats trained with grain-based pellets remained goal-directed over training with this procedure, whereas rats trained with a solution of 20% sucrose rapidly developed habit. The aim of this study was to explain this dissociation. To do so, we compared rewards differing in taste (sweet versus unsweet) and/or in nature (liquid versus solid) in animals food-restricted or water-restricted. We found that motivational stake strongly promotes goal-directed behavior. While responding for liquid rewards is habitual when rats are food-restricted, lever pressing for a sucrose solution is goal-directed under conditions of water-restriction. Switching the motivational state from water- to food-restriction restores the original dissociation with habitual responding for sucrose while lever pressing for food pellet is goal-directed. These results are particularly relevant to understand how homeostatic and nutritional factors can affect the balance between goal-directed and habitual behaviors.

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**Poster**

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**Topic:** G.02. Motivation

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NIDA Grant R01 DA038599

**Title:** Chemogenetic manipulations of prelimbic inputs to the thalamic paraventricular nucleus affect individual differences in response to a reward associated cue

**Authors: *I. RIVERO-COVELO**[1], P. CAMPUS[4], B. N. KUHN[5], S. A. LOPEZ[2], S. M. FERGUSON[6], S. B. FLAGEL[3]
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**Abstract:** Cues that predict the presence of natural rewards can acquire incentive motivational value in addition to predictive value. Notably, cues that acquire incentive motivational value can gain inordinate control over behavior, often leading to maladaptive tendencies such as drug addiction. During a Pavlovian conditioned approach task, in which the presentation of a lever

precedes delivery of a food reward, some rats, termed sign-trackers (STs), approach the lever; while others, termed goal-trackers (GTs), approach the food cup. For STs, the cue becomes an incentive stimulus; whereas for GTs it is merely a predictor. Recently, we have shown that the paraventricular nucleus of the thalamus (PVT) is involved in the regulation of sign- vs. goal-tracking behavior. Selective lesions of the PVT enhance sign-tracking behavior, but this nucleus appears to serve distinct functions in STs and GTs. Relative to GTs, STs show enhanced c-fos expression in the PVT in response to a discrete cue previously paired with food- or drug-reward. Further, for STs, cue-induced c-fos in the PVT correlates with cue-induced c-fos in subcortical regions; whereas for GTs, cue-induced c-fos in the PVT correlates with that in the prelimbic cortex (PrL). Thus, we postulate that the PVT acts as a central node to regulate the attribution of incentive motivational value to reward cues, and that inputs to the PVT from the PrL may inhibit this process. Here, we interrogated the role of this circuit in sign- and goal-tracking behaviors using a dual vector approach to selectively express Designer Receptors Exclusively Activated by Designer Drugs (DREADD) in PrL projections to the PVT. A Cre-dependent viral vector expressing inhibitory Gi or stimulatory Gq DREADD was infused into the PrL, while a CAV-Cre viral vector was injected into the PVT. This resulted in DREADD expression only in PrL-PVT neurons. In GTs, there was no apparent effect of chemogenetic manipulation of the circuit. In contrast, in STs, CNO stimulation of Gi signaling in PrL-PVT neurons increased goal-tracking behavior, while leaving sign-tracking behavior intact. Interestingly, CNO stimulation of Gq DREADD decreased the conditioned reinforcing properties of lever-cue, but did not affect sign- or goal-tracking behavior. Thus, “turning off” or “turning on” the PrL-PVT circuit has differential effects on cue-motivated behaviors that depend on individual variation in the attribution of incentive motivational value to the cue and the way in which this is assessed. Taken together, these data suggest that top-down processes from the PrL to the PVT may be a critical component of cue-motivated psychopathologies, like addiction.

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**Poster**

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**Topic:** G.02. Motivation

**Support:** NIDA R01 DA038599

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**Title:** The role of cortico-thalamic circuitry in the reinstatement of drug-seeking behavior

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**Abstract:** One of the biggest challenges for the treatment of addiction is relapse, with rates as high as 90%. Relapse is often triggered by cues in the environment (e.g. people, places and paraphernalia) that were previously associated with the drug-taking experience. Thus, in order to better treat relapse, it is imperative to understand the neurobiological mechanisms by which cues in the environment are able to gain inordinate control and lead to maladaptive behaviors. One brain region that has recently been recognized for its role in cue-induced drug-seeking behaviors is the paraventricular nucleus of the thalamus (PVT). The PVT sits at the interface of cortical, limbic and motor pathways, putting it in an ideal location to regulate motivated behaviors, such as drug-taking and drug-seeking behavior. Recent work from our lab suggests that the PVT plays an important role in mediating individual differences in the propensity for cue-induced relapse. However, the specific PVT circuitry mediating this variation in drug-seeking behavior remains unknown. The prelimbic cortex (PrL) is one region that sends dense projections to the PVT and this brain region has been implicated in addiction-related behaviors in both pre-clinical and clinical neuroscience studies. Data from our lab suggests that the PrL-PVT pathway plays an important role in the motivational properties of reward-associated cues. Thus, the aim of the current study is to determine if the PrL-PVT pathway is important for cue-induced drug-seeking behavior. To assess this, we used a dual-vector DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technique that allowed us to specifically assess the effects of inhibiting (Gi-DREADD) the PrL-PVT pathway on cue-induced and cocaine-induced drug-seeking behavior, or reinstatement. Rats underwent 2 weeks of cocaine self-administration followed by 4 weeks of abstinence and then extinction training. Prior to the test for cue-induced and cocaine-primed reinstatement, rats received an injection of vehicle or clozapine-N-oxide (CNO) to activate the inhibitory $G_i$-DREADD. CNO-induced inhibition of the PrL-PVT pathway decreased cocaine-seeking behavior during cue-induced reinstatement, but had no effect during cocaine-primed reinstatement. Thus, the PrL-PVT pathway appears to play a specific role in cue-mediated drug-seeking behavior. The role of this pathway in mediating individual variation in the motivational value of a drug cue is being assessed in ongoing studies. These findings have the potential to further our understanding of the neurobiological mechanisms mediating relapse, and can lead to novel targets for the treatment of addiction.

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**Poster**

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**Topic:** G.02. Motivation

**Support:** P01 DA031656

**Title:** The encoding of incentive salience in the ventral pallidum

**Authors: *A. M. AHRENS**, T. E. ROBINSON, J. W. ALDRIDGE
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**Abstract:** Some rats naturally attribute incentive salience to a conditioned stimulus (CS) paired with food reward (sign-trackers, STs), while others respond primarily to the predictive value of a cue (goal-trackers, GTs). Sign-tracking is associated with greater cue-induced activation of mesolimbic structures than goal-tracking; however, it is unclear how features of the CS itself might influence the engagement of incentive-related neural pathways. Our goal was to determine how different cue modalities affected the neural encoding of incentive salience within different subregions of the ventral pallidum. We recorded neural activity as rats performed a two-CS Pavlovian conditioned approach task, in which both a lever CS and a tone CS predicted identical food reward. The lever CS elicited sign-tracking in some rats (STs) and goal-tracking in others (GTs); whereas the tone CS elicited only goal-tracking in all rats. In STs, the lever CS elicited robust changes in neural activity in both anterior and posterior regions of the VP, though the direction of the response varied between regions, with primarily inhibition in the anterior VP and a mix of excitation and inhibition in the posterior VP. These changes were not seen when STs were exposed to the tone CS, and in GTs there were no differences in firing between lever and tone CSs. These results show that the entire VP structure encodes incentive signals, and that neural changes in the VP are only observed when a cue has features that promote the attribution of incentive salience in predisposed individuals.

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**Topic:** G.02. Motivation

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**Title:** Neural representation of sensory-state value in the stratal striosome compartment

**Authors: *T. YOSHIZAWA**, M. ITO, K. DOYA
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**Abstract:** The striatum consists of the striosome (patch) and matrix compartments. It was previously hypothesized that the striosome represents state values, whereas the matrix represents the action values or performs action selection. While previous electrophysiological studies have shown that the striatal neurons represent these variables, it has been difficult to discriminate which striatal compartment each neuron belongs to. In this study, we employ cell-type specific calcium imaging and endoscopic microscopy to test whether striosome neurons represent value information.

We used the transgenic mice expressing Cre recombinase selectively in striosome neurons (Gerfen *et al.*, 2013). To express GCaMP6s selectively in striosome neurons, we injected AAV.Syn.Flex.GCaMP6s to their dorsomedial striatum (DMS). After the expression of GCaMP6s, we implanted a GRIN lens to the DMS for endoscopic *in vivo* calcium imaging (nVistaHD, Inscopix). After recovery from the surgeries, mice were classically conditioned with different odor cues that predicted appetitive or aversive outcomes. The possible outcomes were large reward (water 4 µl), small reward (water 2 µl), nothing, or punishment (a puff of air). Within the first 5 days, mice showed predictive licking behavior during the cue and delay period for the odor stimuli associated with a large reward (Early stage). After subsequent conditioning up to 14 days, mice showed different frequencies of predictive licking for large, small, and no rewards (Late stage).

Daily calcium imaging showed that striosome neurons acquired reward-amount-proportional activities during the cue and delay period. These reward predictive activities encode the value of odor stimulus. In addition, some striosome neurons acquired responses during reward presentation period. Intriguingly, most neurons showed these activities specifically in the Early or Late stage. Compared to the control group neurons recorded non-selectively, the striosome neurons more strongly encoded the reward-related value and reward information in the Late stage ($p<0.05$, $\chi^2$-test). In the striosome, the proportions of reward-predictive and responsive neurons were 19% (23 of 123 neurons) and 23% (28 of 123), respectively. In the control, they were 8% (7 of 83) and 7% (6 of 83).

These findings are consistent with the hypothesis that the striosome takes the role of the critic that evaluates the value of sensory state in reinforcement learning. A novel unexpected finding is that the striosome consists of learning-stage-specific-neural ensembles. The results suggest that the striosome takes a more dominant role in reward prediction than the matrix after sufficient learning.

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**Poster**

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**Topic:** G.02. Motivation

**Support:** NIAAA IRP

**Title:** Nucleus accumbens serotonergic modulation of risky decision-making

**Authors: *A. POSTLE**[1], L. R. GLOVER[2], A. HOLMES[3]
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**Abstract:** A range of neuropsychiatric disorders, including drug addictions, are characterized by poor decision-making, particularly under conditions when actions can have negative or punished outcomes. The neural mechanisms underlying these abnormal processes are, however, still poorly understood. To address this gap in the literature, we first developed a novel assay for risky decision-making in mice, building on task previously described in rats (Orsini et al. *J Neurosci.* 2015). Mice were trained to reliably touch one visual stimulus on a computer monitor to obtain a large liquid reward, in preference over a simultaneously presented stimulus that produced a small reward when touched. Then, during test sessions, each touch at the large-reward stimulus produced footshock at increasingly probabilities across successive trial-blocks: 0, 25, 50, 75 or 100% probability of shock. The small-reward stimulus was never associated with shock. We first established that female and male C57BL/6J mice reduced preference for the large-reward in a shock-probability dependent manner. Next, we examined the potential contribution of serotonergic transmission in the nucleus accumbens core (NAcc) in modulating risky decision-making. We focused on this system given prior data implicating both the NAcc and serotonin in risk-related behaviors, but a lack of clear evidence to date that determines the possible link between the two. In one experiment, we optogenetically silenced serotonin inputs to the NAcc from the dorsal raphe nucleus, by targeting an AAV carrying halorhodopsin in *SERT*-Cre mutant mice and shining yellow light into the NAcc during behavioral testing. In another experiment, we bilaterally microinfused either the selective serotonin 5-HT2A antagonist, MDL100907, or the 5-HT2C antagonist, SB242064, directly into the NAcc during behavioral testing. We then quantified, using fluorescence *in situ* hybridization, co-expression of 5-HT2A and 5-HT2C with either of the major dopamine receptor subtypes on NAcc medium spiny neurons (MSN), D1DR or D2DR. In addition, we optogenetically silenced either of these classes of dopamine MSN, via targeting of an AAV carrying archaerhodopsin in *D1dr*-Cre and *Adora2a*-Cre mutant mice, respectively, and shining green light into the NAcc during behavioral testing. Our findings provide support for an important contribution of serotonin input to the

NAcc, acting at specific 5-HT2 receptors and possibly in interaction with dopaminergic activity, in risk decision-making. Research supported by the NIAAA IRP.

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**Topic:** G.02. Motivation

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University of Memphis CAS Faculty Research Grant (NWS)

**Title:** Individual differences in risky decision-making predict nicotine sensitivity and other addiction-relevant behaviors

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**Abstract:** Addiction is characterized by persistent risky decision-making in the face of negative consequences. The rodent risky decision-making task (RDT) models this behavior by measuring preference between small, safe rewards and larger rewards with an escalating risk of physical punishment (mild footshock). This task reliably reveals a subset of subjects with an enduring preference for risky rewards, which may provide insight into addiction vulnerability. Here, we characterized rats as “risky” or “non-risky” in RDT, then compared risk preference with other behavioral traits that coincide with addiction. These included: 1.) reinforcer devaluation, which measures habit formation, 2.) DRL 20, which measures impulsive action, 3.) delay discounting, which measures impulsive choice, and 4.) nicotine locomotor sensitization, which assesses behavioral sensitivity to repeated experimenter administered nicotine exposure. First, we observed that risky rats demonstrated a trend toward stronger habit formation compared to safe rats. Risky rats also showed greater impulsive action than safe rats, while there was no relationship between risk preference and impulsive choice. Finally, preliminary data indicate that risky rats were resistant to nicotine locomotor sensitization. Collectively, these data indicate that the RDT reveals a subpopulation of rats with multiple cognitive features that predict vulnerability to addiction, as well as reduced behavioral sensitivity to nicotine exposure.

**Disclosures: D.B. Gabriel:** None. **T.G. Freels:** None. **N.W. Simon:** None.

**Poster**

**512. Reward: Motivational Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 512.14/RR3

**Topic:** G.02. Motivation

**Support:** Brain Behavior Research Foundation Young Investigator NARSAD (NWS)

The University of Memphis CAS Faculty Research Grant (NWS)

**Title:** The effects of enhanced cannabinergic signaling on risky decision-making in rodents

**Authors: *T. FREELS**[1], D. B. GABRIEL[1], N. W. SIMON[2]
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**Abstract:** Suboptimal decision-making and aberrant cannabinoid signaling are both prevalent in psychopathology. However, little is known about the cannabinergic mechanisms of decision-making guided by risk of punishment. The Risky Decision-making Task (RDT) measures preference between a small, safe reward and a large reward accompanied by an escalating probability of foot shock. We tested the acute effects of multiple doses of systemic AA-5-HT, a fatty acid amide hydrolase inhibitor that enhances endocannabinoid tone, and the selective CB1 agonist ACEA on RDT performance in male Long-Evans rats. We found that neither AA-5-HT nor ACEA affected overall risk preference or omissions in RDT. Interestingly, we found that both cannabinoid treatments increased decision latency in dose-dependent fashion. This effect does not appear to be related to reduced locomotion, reward motivation, or overall task engagement. In addition, we observed that AA-5-HT increased stereotypy and rearing behavior in the open field without altering overall locomotion or thigmotaxy. Our results suggest that enhancing cannabinergic signaling may engender cognitive inefficiency during decision-making without modulating risk-taking behavior.

**Disclosures: T. Freels:** None. **D.B. Gabriel:** None. **N.W. Simon:** None.

**Poster**

**512. Reward: Motivational Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 512.15/RR4

**Topic:** G.02. Motivation

**Support:** NCRG seed grant 20R75517

**Title:** Eyes on the prize: Risk-promoting sensory reward features result in pupil dynamics consistent with a shift in locus coeruleus-mediated control states

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**Abstract:** The presence of sound stimuli during slot machine play has been found to increase arousal measured by self-report and skin conductance (Dixon et al, 2014). We have recently demonstrated that the presence of reward-paired sensory features (money images and casino-inspired jingles) promotes risk taking on an economic decision making task. Here, we used pupillometry as a proxy of locus coeruleus-mediated arousal to examine whether risk-promoting sensory feedback increases arousal, as well as to explore possible links between arousal and risk. Healthy volunteers were randomly assigned to perform the decision making task either with or without the sensory feedback features, with concurrent pupil tracking. Aside from the feedback, the two task versions were visually identical. We found that baseline pupil sizes at trial onset were larger in the group without sensory features ($p = .008$). This could not be a luminance-driven effect: the baseline displays were identical, and the feedback display had higher luminance without the sensory enhancement (white screen), which should result in smaller, not larger pupil sizes. Conversely, phasic pupil dilation across decision and feedback anticipation phases of the task (measured as area under the curve with respect to trial baseline), was greater in the presence of the sensory features ($p = .01$). Moreover, the magnitude of decision- and anticipation-related phasic pupil responses on a given trial was significantly associated with the likelihood of taking a risk ($ps \leq .0006$). Changes in pupil dynamics in response to sensory task enhancement are consistent with a shift from a more exploration-dominated to a more exploitation-dominated control state, as proposed by the adaptive gain theory of noradrenergic signalling (Aston-Jones and Cohen, 2005). The former is associated with the tonic mode of locus coeruleus activity, characterized by more enduring but less discriminative responsiveness of cortical neurons. The latter is associated with the phasic mode, characterized by more selective increases in neuronal responsiveness to task-relevant stimuli. Reward-paired audio-visual stimuli, which are ubiquitous in electronic gambling, might shift the balance towards a more exploitation-dominated state, where cortical neurons are selectively responsive to game-related stimuli. Heightened phasic responses to task events characteristic of this state appear to be linked to risk taking.

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**Poster**

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**Program#/Poster#:** 512.16/RR5

**Topic:** G.02. Motivation

**Support:** NIDA R01 DA013951

CRAN supplement to NIAAA T32 AA007474

**Title:** The abused inhalant toluene increases risky decision making in a rodent model of probabilistic discounting

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**Abstract:** Volatile organic solvents cause intoxication and neurochemical changes that are similar to classic drugs of abuse. These include transient and persistent changes within several cortical regions including the medial prefrontal cortex (mPFC) that can lead to a loss of "top-down" control of complex behaviors. The mPFC undergoes significant maturation during adolescence and previous studies in our lab have shown that adolescent mPFC neurons are particularly sensitive to toluene. As solvent abusers often show impaired decision making, it is important to understand how toluene affects choice selection, especially when the choice involves uncertainty. To explore this question, we used a well-validated rodent model of risky decision making termed probabilistic discounting (PD) and tested animals on this task after chronic exposure to toluene. To mimic patterns of human toluene intoxication, we treated adolescent male and female Sprague-Dawley rats with twice daily, fifteen minute exposures to toluene vapor (5700 ppm) for five consecutive days (P39-44). After reaching adulthood (P60), rats were trained to lever press for a palatable food reward (20% sweetened condensed milk). One lever delivered a small, certain reward (30 µl, 100% of the time) while a second lever delivered a large, uncertain reward (90 µl, reinforcement probability degrades over 5 successive blocks of 18 trials). Rodents exposed to toluene during adolescence did not show altered risk taking behavior in adulthood, although they did take significantly longer to lever press compared to air treated controls. Interestingly, acute exposure (15 min) of adult animals to toluene (5700 ppm) 45 min prior to PD increased selection of the large/risky lever even when the reinforcement was extremely uncertain. This was due to both increased responsiveness to risky reinforcement and decreased loss aversion. These differences were not observed following exposure to a lower concentration (2850 ppm) of toluene. A previous study in our lab demonstrated that toluene induces an endocannabinoid-mediated long-term depression of glutamatergic synaptic activity in

the mPFC. Ongoing studies are testing the hypothesis that the toluene-induced increase in risky behavior are mediated via endocannabinoid modulation of mPFC activity.

**Disclosures: K.M. Braunscheidel:** None. **S.B. Floresco:** None. **J.J. Woodward:** None.

**Poster**

**512. Reward: Motivational Mechanisms**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 512.17/RR6

**Topic:** G.02. Motivation

**Support:** CIHR

**Title:** vmPFC value signal for high calorie snack foods relates to weight gain in first year students

**Authors: *S. NESELILER**[1], K. LARCHER[2], Y. ZEIGHAMI[2], S. SCALA[2], R. REID[3], R. ANDERSEN[3], A. DAGHER[4]
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**Abstract:** Wanting is the psychological process of incentive salience, through which cues predicting reward acquire subjective value. Increased subjective value for high calorie foods might underlie the neurobiological basis of the vulnerability for obesity. Therefore, increased subjective value for food cues should increase the probability of food intake and subsequently lead to weight gain.
We tested this hypothesis using the Becker DeGroot Marschak auction paradigm (BDM) to assess the subjective value for high calorie versus low calorie food items in first year university students[1]. We utilized the first year university students to study the neurobiological basis of the vulnerability for weight gain since students tend to gain more weight in a short period of time during the first year of university compared to age-matched controls[2]. In addition, for most students this is the first time they are making food decisions independently. Therefore, we predicted that increased subjective value for high calorie food cues would result in increased weight gain in this population.
**Methods**
72 first-year students who were living independently for the first time outside of the family home enrolled in the 8-month long study (mean BMI at entry: 22.6±2.5 SD). Participants underwent fMRI during which they completed the BDM auction task at beginning of the school year. In the BDM task, participants bid on high and low calorie snack foods and trinkets. We measured participants' weight at the beginning and at the end of the school year using a medical scale.

The data was pre-processed using FSL (www.fmrib.ox.ac.uk/fsl)[3]. The BOLD activity to high calorie food cue at high bidding versus low bidding was compared to low calorie food cue at high versus low bidding. Using this analysis, we investigated how the caloric content modulated by subjective value (measured by bidding) interacts with weight gain.

**Results**

There was substantial variability in weight change among our participants (mean weight gain in pounds 3.0± 6.3 SD). In the brain, the caloric content modulated by subjective value interacted with weight gain. Participants with higher weight gain showed increased BOLD in left vmPFC (T-value=3.4, MNI: X=-8, Y=38, Z=-10) and left medial OFC (T-value= 3.2, X=-4, Y=48, Z=-10).

**Conclusions**

Increased value-related activation in the vmPFC was correlated with weight gain in first year university students. This result suggests that increased activation in an area that is known to compute subjective value exhibited might underlie the neurobiological basis of the vulnerability to weight gain and obesity.

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**Poster**

**512. Reward: Motivational Mechanisms**

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**Topic:** G.02. Motivation

**Support:** NIMH U54 HD079124

Autism Science Foundation Grant 16-001A

**Title:** Intranasal oxytocin increases reward circuitry responses to monetary rewards in children with autism

**Authors: *R. K. GREENE**[1], C. ALDERMAN[4], M. SPANOS[4], E. WALSH[2], J. BIZZELL[4], G. D. STUBER[5], L. SIKICH[4], G. S. DICHTER[3]
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**Abstract:** Background: Oxytocin (OT) administration has been shown to improve social symptoms of individuals with autism spectrum disorder (ASD); however, the mechanism of action behind this effect is unclear. Although evidence suggests that these behavioral changes

may be attributed to the effect of OT on the mesolimbic dopamine system, no study to date has examined the effect of OT on this specific neural system. Additionally, whether OT impacts responses to social reward specifically has not been investigated. Therefore, this study examined the effects of a single dose of intranasal OT on neural responses to social and nonsocial rewards in adolescents with ASD.
Methods: In this placebo-controlled double-blind study, twenty-nine adolescents with ASD (age: *M*=13.38 years, *SD*=2.32) completed two fMRI scans, one after OT administration and one after placebo administration. During each scanning session, participants completed social and monetary incentive delay tasks, which required that participants press a button as quickly as possible after seeing a reward availability cue. If a button was pressed quickly enough participants would "win" either a monetary reward (represented by an image of currency) or social reward (represented by an image of a happy, direct-gaze face).
Results: Analysis of the anticipatory phase of the monetary condition revealed greater activation in the right nucleus accumbens (NAcc), the left putamen, and the anterior cingulate gyrus (ACgG) during the OT condition compared to the placebo condition. Alternatively, analyses of the anticipatory phase of the social reward condition showed no significant increase in activation during the OT condition compared to the placebo condition. To investigate the effects of OT on brain activation to social versus nonsocial rewards, we evaluated a drug condition x reward type interaction. The right NAcc and the left putamen showed greater activation during nonsocial relative to social reward anticipation after intranasal OT administration relative to placebo. Additionally, these analyses revealed greater activation during nonsocial relative to social reward outcome phase after OT relative to placebo administration in the right orbital frontal gyrus and the ACgG.
Conclusions: Results suggest that the effects of intranasal OT administration in ASD may not be constrained to social processing systems, but rather may extend more generally to mesocorticolimbic brain systems that control incentive salience processing, reward valuation, and reward-based learning.

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**Poster**

**512. Reward: Motivational Mechanisms**

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**Topic:** G.02. Motivation

**Support:** NEI RO1-025872

James S. McDonnell Foundation award

HHMI International Fellowship

**Title:** Reward and selection history shape neural representations of an attentional priority in human visual and parietal cortex

**Authors: *S. ITTHIPURIPAT**[1], V. A. VO[1], T. C. SPRAGUE[3], J. SERENCES[2]
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**Abstract:** Many prominent theories of attention highlight a dichotomy between the top-down and bottom-up control of attention. However, this dichotomy fails to account for many situations where goal-directed behaviors are disrupted by attentional capture that is induced by task-irrelevant distractors associated with reward. This observation supports an alternative framework, which posits that reward and selection history can interact with current behavioral goals in an integrative attentional priority map. While there is strong behavioral evidence in support of this view, less is known about how reward and selection history shape priority signals across cortical areas in the visual hierarchy. Here, we measured neural activity in visual and parietal cortex using functional magnetic resonance imaging (fMRI) while human subjects were performing a value-based decision-making task. During the scan, subjects learned values associated with the colors of visual targets presented at two spatial locations, while ignoring a task-irrelevant distractor in the third location. Across trials, the color associated with each visual stimulus was swapped across three different locations so that we could examine behavioral and neural effects of target and distractor values based on their selection history. We found that target selection bias (i.e., the probability of choosing high-valued over low-valued targets) decreased and response times increased as distractor value increased. Using a multivariate image reconstruction analysis of the fMRI data, we found that distractor value and selection history jointly modulate the gain of spatial representations centered at the distractor location, and such modulations occurred across many retinotopically organized regions of visual and parietal cortex. Importantly, these gain modulations also appeared to modulate the degree of representational bias between selected and unselected target locations. Overall, these results suggest that value-based decision-making is supported via the interaction between reward-based gain modulations of neural representations related to both task-relevant and task-irrelevant stimuli.

**Disclosures: S. Itthipuripat:** None. **V.A. Vo:** None. **T.C. Sprague:** None. **J. Serences:** None.

**Poster**

**512. Reward: Motivational Mechanisms**

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**Topic:** G.02. Motivation

**Support:** Lieber Institute for Brain Development

National Institute of Mental Health Intramural Research Program

**Title:** Using expectancy theory to quantitatively dissociate human neural activation for motivation from that of reward-related factors

**Authors: A. KOHLI**, R. W. LEFCO, *C. F. ZINK
Lieber Inst. For Brain Develop., Baltimore, MD

**Abstract:** Much research has been dedicated to deciphering the neural correlates of motivation and reward processes in the human brain. It has been difficult, however, to attribute neural signals precisely to motivation disentangled from experimentally-manipulated factors that influence motivation. We overcome this challenge with the novel application of an operational theory of motivation, namely the Expectancy Theory (ET), to human fMRI data. The use of ET enables the isolation of activity precisely corresponding to motivation distinct from other factors, including reward magnitude, reward probability, task difficulty, and expected value. According to ET, motivational force (MF), a force that energizes behavior and determines the level of effort to put forth on a given task, is the product of three factors: 1) Expectancy (E) - the belief that increasing effort will increase performance (i.e., success probability/task difficulty); 2) Instrumentality (I) - the belief that increased performance leads to a particular outcome (i.e., outcome probability); and 3) Valence (V) - the extent to which the outcome is desired (i.e., reward magnitude/value). Here, during fMRI, two groups of 50 healthy subjects (n = 100) performed a modified version of the Monetary Incentive Delay task that was designed to isolate neural activity corresponding to each ET variable by assigning cue-predicted task difficulty, reward probability, and reward magnitude in particular combinations. Voxels were classified as activating in response to a particular ET variable based on the relative activation pattern exhibited across cue type. Specifically, average beta estimates for each cue type were extracted from each voxel in the group whole-brain mask, statistically compared using two-tailed, paired t-tests between cue types, and mapped to ET variables according to particular patterns. Subsequently, the ET variable associated with any voxel was only reported if it was replicated between the two groups, with the resultant variable cluster extent > 5 voxels. We find significant signals in the midbrain, ventral striatum, motor cortex, and visual cortex that specifically map to motivation (i.e., MF), rather than other reward-related factors that map to other regions in the brain, such as insula, amygdala, cingulate, premotor, parietal, prefrontal, and orbitofrontal areas. This is important because it clarifies the long-standing confounding nature of motivation versus reward in these signals. It also highlights the practicality and effectiveness of the application of ET to neurobiology to more precisely and accurately probe motivation neural correlates than has been achievable previously.

**Disclosures:** **A. Kohli:** None. **R.W. Lefco:** None. **C.F. Zink:** None.

**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 513.01/RR10

**Topic:** G.01. Appetitive and Aversive Learning

**Support:** NIMH grant R01-MH083710 to DP

NIMH grant R01-MH087755 to SN

**Title:** Central amygdala model integrates intra-amygdalar inputs during fear conditioning

**Authors: *B. LATIMER**[1], P. SAMARTH[1], F. FENG[1], D. PARE[2], S. S. NAIR[1]
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**Abstract:** Classical fear conditioning (FC) leads to potentiation of conditioned stimulus (CS) inputs to lateral amygdala (LA) neurons, and to increases in the firing of central medial amygdala (CeM) cells. In turn, CeM cells drive conditioned fear responses via their projections to fear effector neurons. However, transmission of information from LA to CeM neurons is indirect, involving basal amygdala (BA), the central lateral (CeL) nucleus, and intercalated cells (ITC), all of which project to CeM. Although CeM is thought to be the main fear output station of the amygdala for conditioned fear responses, the details of connectivity within Ce are not well understood. LA axons contact CeL but not CeM cells, and it is not clear how LA influences CeM through CeL. Also, CeL contains two types of CeM-projecting cells, with inhibitory (CeL-Off) and excitatory (CeL-On) responses to the CS. These two cell types inhibit each other and it was hypothesized that the inhibition of -Off cells by -On cells leads to the disinhibition of CeM cells. However, it is not clear whether LA and BA inputs connect differently to the two CeL cell subtypes and whether intrinsic and afferent synapses to Ce can undergo activity-dependent plasticity.
We developed a 500-cell biophysical model of CeL and CeM to investigate how Ce might integrate afferents from LA, BA and ITC during FC. All afferents are modeled as spike trains using experimental tone response data. The network had experimental estimates of regular spiking (RS) and low-threshold bursting (LTB) cell proportions, and of intrinsic connectivity. Starting with 6% unbiased connectivity for all afferents to CeL, we tuned the connection weights to match both habituation and tone-induced *in vivo* responses: 8% (19/240) of the model CeL cells showed CS-evoked increase (-On) and 9% (22/240) showed CS-evoked decrease in firing rates (-Off) during habituation; the numbers after conditioning were 17% and 14%, respectively. Analysis of connectivity for CeL cells revealed that the only significant difference in connectivity for -Off cells compared to -On cells was from ITC afferents. Further investigation of –Off cells showed that although they were not predominantly of the PKCδ+ type, biasing ITC connections to PKCδ+ vs. PKCδ- type (9 and 6 % vs the original unbiased 6 and 6%) resulted in

82% of the –Off cells being from the PKCδ+ group. Another observation was that a larger proportion of LTB cells, compared to RS cells, were of the –Off type after training, although both types are equally probably of being PKCδ+ or PKCδ-. Tone-induced firing of LTB cells was delayed compared to that of RS cells, suggesting that inhibition from RS cells may add to LTB cells becoming –Off cells.

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**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

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**Program#/Poster#:** 513.02/RR11

**Topic:** G.01. Appetitive and Aversive Learning

**Support:** NIMH Grant R01 MH107239

**Title:** Differential recruitment of competing valence-related amygdala networks during anxiety

**Authors: *S.-C. LEE**[1,2], A. AMIR[1], D. HAUFLER[1], D. PARE[1]
[1]Neurosci., Rutgers Univ., Newark, NJ; [2]Neurosci., Johns Hopkins Univ., Baltimore, MD

**Abstract:** The basolateral amygdala (BL) is involved in fear and anxiety but it is currently unclear how the same network supports these two states. To address this question, we trained rats on appetitive and aversive conditioning in different contexts. Distinct groups of BL neurons displayed increased activity during appetitive (CS-R) vs. aversive (CS-S) conditioned stimuli (R-cells and S-cells, respectively) and they were typically inhibited by the other CS. When the CS-S was presented in the safe context, rats entered a long-lasting anxiety-like state characterized by increased inter-CS freezing and impaired reward-seeking. During this state, a subset of BL cells ('state-cells') showed sustained shifts in baseline activity whose time course matched that of the behavioral changes. Many state-cells with increased firing rates were S-cells whereas R-cells only included state-cells with reduced firing rates. Thus, anxiety involves persistent activity changes that are differentially expressed by subsets of valence-specific BL neurons.

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**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 513.03/RR12

**Topic:** G.01. Appetitive and Aversive Learning

**Support:** Korean Ministry of Health grant HT13C0009

**Title:** The brain mapping of contextual fear memory in rats using manganese enhanced MRI

**Authors: *T. LEE**[1], J. YANG[2], M. KIM[1], M. HAN[1], Y. CHANG[2]
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[2]Kyungpook Natl. Univ., Daegu, Korea, Republic of

**Abstract:** The survival of organisms critically depends on avoidance responses to life threating stimuli or situations. Sensory information about the context needs to be remembered to produce defensive behavior in the same situation. To investigate underlying brain regions to encode dangerous contexts, manganese enhanced MRI (MEMRI) was utilized in the contextual fear conditioned rats. MEMRI is widely used to monitor whole brain activities with high resolution images. The paramagnetic manganese ion, as an effective contrast agent, accumulates in neurons via voltage-gated calcium channels and enhances contrast in the activated tissues captured by T1 weighted MRI.
Fear conditioning was conducted in male Sprague-Dawley rats (6-7 weeks old; weighing 160-240g). The animals were exposed to a conditioning box for an hour. Electric foot shock (1mA 0.5sec duration) was delivered to the floor grid every 3 minutes (total 20 shocks). Control animals were exposed to the same context without foot shocks. The animals received nasal injection of manganese chloride (0.2 mM/kg body weight) dissolved in saline to monitor brain areas involved in olfactory cues of the context. Forty-eight hours after the conditioning, rats were exposed to the same conditioning environment for 10 minutes to test contextual fear memory. Under isoflurane anesthesia, their brains were scanned with Bruker 9.4T MRI. Acquired images were processed and statistical analyses were performed using SPM8. Brain activation maps related to fear conditioning between groups were generated by two sample analysis.
MRI signal enhancement in fear conditioned rats was observed in the olfactory tubercle, amygdala, somatosensory cortex, Caudate putamen (Cpu), granular and dysgranular insular cortex. Nasal injection of manganese produced greater signal enhancement in the olfactory tubercle indicating olfactory processing of the context. The activations in the granular insula cortex, dysgranular insular cortex suggest that the insular cortex plays a key role in pain processing. The activation in Cpu was related to the experience of pain, the coordination of context-dependent movement. Activations in the amygdala, olfactory tubercle and sensory cortex indicates MEMRI detects brain activations related to conditioned fear. Specifically, the olfactory

context cue relayed by olfactory tubercle and foot shock information processed by sensory cortex merge and form fear memory in the amygdala. We employed an activity-dependent MEMRI technique to reveal fear circuits related to the odor context cue.

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**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

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**Topic:** G.01. Appetitive and Aversive Learning

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**Title:** Human functional, structural, and biochemical neuroimaging of acute post-traumatic stress

**Authors: *N. G. HARNETT**[1], E. W. FERENCE, III[2], K. H. WOOD[1], M. A. REID[4,3], M. D. WHEELOCK[1], A. C. LAHTI[3], A. J. KNIGHT[2], D. C. KNIGHT[1]
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**Abstract:** Although traumatic events are experienced by over 50% of the U.S. population, only a portion of traumatized individuals develop a subsequent stress disorder. Susceptibility to trauma-induced stress disorders may be mediated by variability in human neurobiology. Prior human neuroimaging research has observed alterations in the function, structure, and biochemistry of a prefrontal cortex (PFC) - amygdala network in individuals with chronic Post-Traumatic Stress Disorder (PTSD). However, the relationship between the neurobiology of the PFC - amygdala network and acute post-traumatic stress remains unclear. Understanding the neurobiology of acute post-traumatic stress may elucidate the etiology of PTSD, and provide quantifiable neural markers for the prediction and prevention of PTSD. Twenty-one trauma-exposed (TE) and nineteen non-trauma-exposed (NTE) volunteers participated in a multidimensional neuroimaging study. Data included structural (diffusion weighted scans), biochemical (1H magnetic resonance spectroscopy), and functional (blood-oxygen-level-dependent; BOLD) images acquired during a Pavlovian fear conditioning procedure. Tractography analyses of the diffusion weighted data revealed the white matter microstructure of both the uncinate fasciculus and fornix/stria

terminalis varied with acute post-traumatic stress severity. Biochemical scans assessed neural glutamate (Glx) levels within dorsal anterior cingulate cortex (ACC). Glx concentrations measured acutely varied positively with both acute and 3 month follow-up post-traumatic stress severity. In addition, functional imaging revealed differences in the dorsal ACC response to safety cues such that the TE group exhibited greater activity compared to the NTE group. Further, the TE group demonstrated altered safety-learning compared to the NTE group indexed via UCS expectancy. Taken together, the present findings suggest 1) trauma exposure may be related to acute changes in the neural substrates that support fear learning processes, 2) microstructure of white matter tracts connecting the PFC and amygdala may be related to development of PTSD, and 3) glutamate within dorsomedial PFC may play an important role in post-traumatic stress. The present study extends our understanding of the neurobiology associated with post-traumatic stress in a unique population, and sheds new light on the etiology of PTSD.

**Disclosures: N.G. Harnett:** None. **E.W. Ference:** None. **K.H. Wood:** None. **M.A. Reid:** None. **M.D. Wheelock:** None. **A.C. Lahti:** None. **A.J. Knight:** None. **D.C. Knight:** None.

**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 513.05/RR14

**Topic:** G.01. Appetitive and Aversive Learning

**Support:** Swiss National Science Foundation

Olga-Mayenfisch Foundation

**Title:** Neural computations underlying human Pavlovian threat learning

**Authors: *K. E. OJALA**[1,2], A. TZOVARA[1,2], D. R. BACH[1,2,3]
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**Abstract: Introduction.** Reinforcement learning (RL) theory describes how expectations and their violations (prediction errors, PE) might drive learning. Appetitive learning and PEs have been studied extensively but as of yet we have little information on where and how aversive prediction errors might be computed. Here, we sought to delineate human brain regions that encode different types of aversive PEs and learning-related signals by using functional magnetic resonance imaging (fMRI) and Pavlovian threat learning (fear conditioning) with partial reinforcement.

**Methods.** 22 participants underwent fMRI scanning at 3T. The conditioned stimuli (CSs) in the experiment were triangles with different colours corresponding to different probabilities of receiving an electric shock to the forearm (unconditioned stimulus, US). We used an axiomatic approach to search for brain regions encoding aversive PE signals, separately for positive, negative, and unsigned PEs. We have previously shown that a beta-Bernoulli optimal Bayesian learning model better explains behavioural data than a range of RL models. Hence, we also analysed neural activity relating to trial-by-trial parameters from this model, representing expectation, model update and surprise.
**Results.** In the axiomatic approach, we did not find any brain regions in which BOLD signals unambiguously fulfilled the axioms for representing positive, negative or unsigned aversive prediction errors. In the model-based analysis, we found that expectation of US probability from our learning model was associated with activation in the left anterior insula and opercula of insula. Moreover, prior entropy of shock probability, a measure of uncertainty about US probability that has been previously related to skin conductance responses, was associated with activation in parietal-occipital, superior-medial frontal, and motor regions. Bayesian surprise about the US outcome was encoded in middle dorsal prefrontal cortex. Finally, model update based on the experienced US from the current trial (KL divergence) related to activity in inferior, middle and superior frontal regions as well as in parietal regions during acquisition of the CS-US associations.
**Discussion.** In contrast to previous work on appetitive, and aversive operant, learning, we did not find brain regions axiomatically encoding PE signals during Pavlovian threat conditioning. Instead, we highlight neural activity related to trial-by-trial parameters from an ideal Bayesian observer model that also best explained previous behavioural data.

**Disclosures: K.E. Ojala:** None. **A. Tzovara:** None. **D.R. Bach:** None.

**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

**Location:** Halls A-C

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**Program#/Poster#:** 513.06/RR15

**Topic:** G.01. Appetitive and Aversive Learning

**Support:** National Science Foundation grant BCS 1460909

**Title:** The neuroimaging of human fear conditioning: Quantitative seed-based and linguistic meta-analyses

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**Abstract:** The application of fear conditioning across organisms and techniques has begun to detail the neurobiological mechanisms through which fears are acquired and extinguished. These efforts are likely to yield greater insight into anxiety and fear disorders for which aberrant threat processing and regulation contributes to their etiology and persistence. Key in advancing our understanding of fear conditioning is the ability to synergize results across studies to test the consistency of findings. To date, work across animal models, human neuroimaging, and patient-based studies has identified the amygdala to be critical to fear learning and a key node in a network of cortical and subcortical regions that together form a fear-learning network. However, the amygdala has not consistently emerged in quantitative meta-analytic reviews of human neuroimaging studies. One explanation for this discrepancy may be the reliance on whole-brain analyses, which may not be sensitive to hemodynamic activation within the amygdala, given its low signal magnitude, susceptibility to magnetic field artifacts, and variability in peak activation location across subjects. Therefore, the aim of the present work was to attempt to resolve this discrepancy by conducting a survey of the human neuroimaging literature from 1998-2017. We focused on meta-analytic methods that can help elucidate the role of the amygdala and other theoretically-implicated regions of interest. Utilizing seed-based *d* mapping (SDM) of peak coordinates from 32 studies using whole-brain analyses, we identified a network of regions frequently implicated across studies of fear conditioning, including the inferior frontal gyrus, cingulate cortex, superior temporal gyrus, insula, and thalamus. Importantly, when we included in the analysis 33 studies that specifically interrogated the amygdala through region-of-interest analyses, we additionally observed consistent activation within right amygdala. Using a complementary linguistic-based meta-analytic approach through term-based mass synthesis of neuroimaging results from the Neurosynth database, we found similar results, including activity in the bilateral amygdala. Our survey illustrates the challenges inherent in aligning results across imaging studies that use different design and analytic strategies and supports the corpus of data from other methods and organisms that reveal a key role for the amygdala in fear learning.

**Disclosures: D. Stjepanovic:** None. **K.S. LaBar:** None.

**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 513.07/RR16

**Topic:** G.01. Appetitive and Aversive Learning

**Title:** Enhancement of auditory processing by classic fear conditioning in humans: Observations from intracranial recordings

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**Abstract:** During classic conditioning, the unconditioned stimulus (US, e.g. a shock) and conditioned stimulus (CS, e.g. a tone) are relayed from the thalamus to the amygdala, both directly and indirectly (through sensory cortices). Different amygdaloid nuclei encode the pairing between CS and US and mediate the expression of the physiological and behavioral response to the US, through the interaction with a wider cortical network.
Here, we recorded human auditory cortex with finely spaced intracranial electrodes in a cohort of 8 patients during a classic conditioning paradigm, using a tone as a CS and a shock as a US. Two tones were presented to the participants: one was paired to the US (CS+), while the other one was never associated to the US (CS-).
At an individual level, 7 out of 8 patients showed an increased power of local field potentials in auditory cortex for the CS+ (CS+ vs. CS-, $p<0.01$ assessed with parametric permutation testing on the power percent change at each time-frequency point). The timing and frequency band was quite variable across patients. Two main types of responses were observed: an alpha power increase around tone onset or a theta power increase around tone offset.
At a group level (considering all 8 patients), the increased response to the CS+ was still present (CS+ vs CS-, $p<0.05$) notwithstanding the individual variability. This increased 'auditory response' was found at both sound onset (in alpha and gamma bands) and offset (theta and gamma) during conditioning. The response was diminished along with the time-course of extinction.
Anatomically, the auditory cortex locations exhibiting a dissociable response were not constrained to a specific region but rather spanned through different locations along the superior temporal gyrus and sulcus.
We suppose that the increase in the power of low frequency components, could relate to an increased attentional bias toward the sound predicting the shock (CS+), while the increased power in higher frequencies could relate to increased local activity.
This could be explained by a plastic change promoted by the amygdala to encode more robustly the CS+. Indeed, the amygdala is believed to modulate cholinergic projections to increase attention and perception toward incoming (conditioned) stimuli. This effect has been characterized as an increased response to the CS in sensory cortex, which has been consistently reported in many animal and human studies.
Our results add evidence to the plastic changes occurring in sensory cortices during classic conditioning, by defining the frequency components and the timing at which an auditory response is most sensitive to the association between the US and CS.

**Disclosures: E. Bartoli:** None. **A.R. Aron:** None. **N. Tandon:** None.

**Poster**

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**Topic:** G.01. Appetitive and Aversive Learning

**Support:** MH078064

MH067564

**Title:** Interactions of $GABA_A$ and oxytocin receptors in state-dependent memory

**Authors: *M. MEYER**[1], A. L. GUEDEA[1], K. NISHIMORI[2], G. MACCAFERRI[1], J. RADULOVIC[1]
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**Abstract:** Memories are typically encoded so that they are easily accessible for retrieval. However, the retrieval of some memories formed under stress-, drug- or affect-induced states is impaired unless the brain is in a similar state as it was during encoding. This phenomenon, known as state-dependent memory (SDM), has been implicated in the development of traumatic amnesia, dissociative symptoms of psychiatric illnesses, as well as the persistence of drug addiction. SDM can be modelled pharmacologically, with information encoded and retrieved in a drug-dependent manner. However, beyond psychopharmacological observation, the neurobiological mechanisms of SDM are still not well understood. To identify novel molecular and cellular mechanisms of SDM, we utilized a recently developed pharmacological model consisting of activation of extrasynaptic γ-aminobutyric acid type A receptors ($eGABA_AR$) during contextual fear conditioning. Based upon emerging evidence that this receptor population can be modulated by the oxytocin system, including our findings that SDM was completely abolished by Oxtr knockout, we used chemogentic approaches to determine whether Oxtr are required for SDM encoding or retrieval. We also performed morphological and immunohistological studies to characterize the identity of the putative Oxtr-positive neuronal populations involved in SDM. Together, these experiments suggest that Oxtr, by contributing to the cellular and behavioral functions of $eGABA_AR$, modulate inhibitory neurotransmission in the hippocampus. In addition to elucidating fundamental principles of SDM, this study is likely to have broad implications for $eGABA_AR$ and Oxtr function, which show abnormalities in most major psychiatric disorders and are important targets for psychopharmacological interventions.

**Disclosures:** **M. Meyer:** None. **A.L. Guedea:** None. **K. Nishimori:** None. **G. Maccaferri:** None. **J. Radulovic:** None.

**Poster**

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**Topic:** G.01. Appetitive and Aversive Learning

**Support:** NIMH Grant MH078064

Davee Award

**Title:** Altered network oscillatory activity in oxytocin receptor knockout mice

**Authors: *K. A. CORCORAN**[1], M. MEYER[2], K. NISHIMORI[3], J. M. RADULOVIC[1]
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**Abstract:** Memories encoded during certain cognitive, affective, pharmacological, or other brain states can often be retrieved only when the brain is returned to the same state present during encoding. We have recently shown that such state-dependent learning requires the activation of extrasynaptic GABAa receptors (eGABAaR) in the dorsal hippocampus (DH); in wild-type (WT) mice, intra-hippocampal administration of the eGABAaR agonist gaboxadol (GBX) prior to fear conditioning yields a memory that can only be retrieved when mice are tested on GBX. In keeping with the role for inhibitory synaptic neurotransmission in the generation of network oscillatory activity, GBX also induces robust changes to local field potentials (LFPs) in DH. eGABAaR colocalize with oxytocin receptors (OxtR) in the dentate gyrus, and can also be activated by oxytocin, but it is not known whether OxtR signaling alone or interactions between these neurotransmitter systems contribute to hippocampal oscillations. To examine this, we tested WT and OxtR knockout (OxtR venus) mice for differences in baseline and GBX-induced patterns of local field potentials in DH. Close interactions between OxtR and eGABAaR suggest that treatments targeting these systems could have significant potential for ameliorating trauma-related dissociative symptoms.

**Disclosures: K.A. Corcoran:** None. **M. Meyer:** None. **K. Nishimori:** None. **J.M. Radulovic:** None.

**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

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**Topic:** G.01. Appetitive and Aversive Learning

**Support:** NIMH Grant R00MH096746

CMS RFUMS start-up funds

**Title:** Corticotropin-releasing factor (CRF) neurons in the oval nucleus of the bed nucleus of the stria terminalis ($BNST_{ov}$) modulate fear and anxiety in rats

**Authors: *A. N. ROMAN**[1], D. MARTINON[1], J. A. DABROWSKA[1,2]
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**Abstract:** Corticotropin-releasing factor (CRF) is a neuropeptide responsible for regulating the autonomic, endocrine, and behavioral responses to stress. One significant population of CRF cell bodies is located within the oval nucleus of the bed nucleus of the stria terminalis ($BNST_{ov}$), a region of the brain that mediates adaptive responses to stressors, such as fear and anxiety. This research investigates the role of these CRF neurons in the $BNST_{ov}$ regarding the acquisition of conditioned cued and non-cued fear. We used designer receptors exclusively activated by designer drugs (DREADDs) within adult transgenic CRF-Cre rats (developed by Pomrenze et al., 2015) to modulate this system. In this model, Cre recombinase is exclusively expressed by CRF neurons. We performed bilateral $BNST_{ov}$ injections of viral vectors driving Cre-dependent expression of DREADDs and reporter protein, mCherry, in both Cre+ and Cre- rats. Viruses used encoded either DREADDs-Gi (pAAV-hSyn-DIO-hM4D(Gi)-mCherry(AAV8)) to silence CRF neurons or DREADDs-Gq (pAAV-hSyn-DIO-hM43(Gq)-mCherry(AAV8)) to activate them. Four weeks after stereotaxic AAVs injections, we measured baseline acoustic startle reactivity of all rats. Then, we used a fear-potentiated startle (FPS) paradigm to determine if activation or inhibition of the CRF neurons in the $BNST_{ov}$ affects cued and non-cued fear in the FPS. The DREADDs selective ligand, clozapine-N-oxide (CNO, 1 mg/kg/mL, IP), was administered prior to fear conditioning. Rats were tested for FPS expression 24 hours later. In order to confirm DREADDs expression, we used striatal-enriched protein tyrosine phosphatase (STEP), which selectively colocalizes with $BNST_{ov}$ CRF neurons. We confirmed through fluorescent immunohistochemistry that mCherry was exclusively expressed on CRF neurons in the $BNST_{ov}$. This mCherry expression was found on neuron membranes, dendrites, spines and axons. We also found that activating or inhibiting CRF neurons in the $BNST_{ov}$ modulates cued and non-cued fear measured in FPS in distinct ways. In light of this data, future experiments will aim to further elucidate the functional role of CRF neurons in the $BNST_{ov}$ and confirm the

specificity of DREADDs expression in this promising animal model. This work is supported by a National Institute of Mental Health grant (R00MH096746) and CMS RFUMS start-up funds to JD.

**Disclosures:** **A.N. Roman:** None. **D. Martinon:** None. **J.A. Dabrowska:** None.

**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

**Location:** Halls A-C

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**Program#/Poster#:** 513.11/RR20

**Topic:** G.01. Appetitive and Aversive Learning

**Support:** COGNITO Grant, Danish Research Council

**Title:** Bidirectional interactions between basolateral amygdala and prefrontal cortex: Implications for development of novel anxiolytics and antidepressants

**Authors: *V. VALENTINI**[1,2], D. PHENIS[2], N. A. CAPACI[2], J. D. MIKKELSEN[3], J. P. BRUNO[2]
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**Abstract:** The basolateral amygdala (BLA) and medial prefrontal cortex (mPFC) have extensive bidirectional connections mediating the bottom-up and top-down processes that regulate affective memory. Dysregulations in these interactions are believed to contribute significantly to the etiology of affective disorders such as depression and anxiety. Previously, we have used NMDA-induced activation of the nucleus accumbens shell (NACshell) to reveal a cholinergic-glutamatergic link that may contribute to top-down regulation of attentional processing. In the current study, after achieving stable baselines we activated the BLA with reverse dialysis perfusion of NMDA (250 uM, 1 hr) and simultaneously measured (20 min collection intervals) changes in the levels of 5 different neurotransmitters in the mPFC and BLA of the same animals. BLA activation resulted in significant increases in extracellular levels (expressed as mean maximum increase above baseline) in DA (97 ± 30%), ACh (55 ± 17%), and glutamate (58 ± 36%) in mPFC. BLA activation did not significantly affect 5-HT (19 ± 15%) or GABA (23 ± 17%) levels. Because our previous experiments with NACshell activation and prefrontal levels revealed that increases in cortical glutamate were secondary to elevations in cortical ACh and stimulation of alpha7 receptors located on glutamatergic terminals, we determined the effects of intra-cortical perfusions of the alpha7 nicotinic antagonist alpha-bungarotoxin (BGT; 1.0 uM) on the intra-BLA-NMDA-induced increases reported above. Administration of BGT effectively blocked the NMDA-induced increases in cortical DA, Glutamate, and ACh. Perfusions of NMDA into the BLA also produced local increases in DA (78 ± 43%) and ACh (103 ± 42%)

within the BLA. Again, these changes were completely blocked by intra-cortical BGT perfusion - suggesting a corticofugal origin for evoked DA and ACh within BLA. To our knowledge, the ability of BLA stimulation to evoke cortical ACh levels, the top down stimulation of local DA and ACh levels in BLA, and the dependence of these bidirectional loops on alpha7 nicotinic receptors are novel observations. These neurochemical results following pharmacological activation of otherwise resting animals will be contrasted with those seen following a more naturalistic behavioral activation of this BLA-PFC circuit during the acquisition and extinction of trace fear conditioning. Collectively, the demonstration of how activity within these bidirectional loops changes as a function of different behavioral states may provide a justification for alpha7 antagonists in the treatment of affective disorders.

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**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 513.12/RR21

**Topic:** G.01. Appetitive and Aversive Learning

**Title:** Brain mechanisms mediating punishment-induced suppression of responding for ethanol

**Authors: *L. R. HALLADAY**, A. KOCHARIAN, A. HOLMES
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**Abstract:** Alcohol use disorders (AUDs) are often characterized by persistent alcohol intake despite harmful consequences. The inability of aversive consequences to reduce drinking behaviors in those with AUDs may be due to an impairment in the neural mechanisms regulating punished behaviors. Past studies have shown that areas of the prefrontal cortex, amygdala, and nucleus accumbens are important for aspects of drug seeking and behavioral flexibility. However little is known about the role of these regions in mediating punished alcohol-seeking. To examine this, we implanted chronic microelectrodes in the prelimbic (PL) and infralimbic (IL) subregions of the prefrontal cortex, the basolateral amygdala (BLA) and nucleus accumbens shell (NAc) to record neuronal activity in freely-moving mice performing a punished-suppression of alcohol-seeking task. Mice were first trained to lever press in order to obtain an alcohol reward, and then during subsequent probe-tests, subjected to a mild footshock when the lever was pressed. Neural recording data revealed several populations of cells that significantly changed their firing rate either during drinking or responding on the lever. Notably, during punished probe-tests, a sub-population of cells in IL significantly increased their firing rate when animals approached the reward lever but did *not* press it, suggesting a role for IL in the inhibition

of responding in the face of negative outcomes. Optogenetic silencing of cells in IL confirmed this role. These data demonstrate neuronal encoding of punished alcohol-seeking in distinct neural ensembles and suggest that resistance to the suppression of alcohol-seeking seen in AUDs may be related to aberrant activity in the IL cortex.

**Disclosures: L.R. Halladay:** None. **A. Kocharian:** None. **A. Holmes:** None.

**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

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**Topic:** G.01. Appetitive and Aversive Learning

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**Title:** Conditioned taste aversion learning drives synaptic depression in rat primary gustatory cortex

**Authors: *M. HALEY**, A. FONTANINI, A. MAFFEI
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**Abstract:** Conditioned taste aversion learning (CTA) is a learning paradigm in which an animal learns to dislike an appetitive, novel taste after it has been paired with gastric malaise. This form of learning is hypothesized to depend on plastic changes in the functional connection between the basolateral amygdala (BLA) and the primary gustatory cortex (GC), as well as plasticity within GC. However, to assess the role of plasticity in CTA learning it is first necessary to determine how CTA learning affects GC circuit activity and physiology, and to gain a deeper understanding of the capacity for plasticity at BLA-GC synapses. Here we used CTA training and an optogenetic approach combined with whole-cell patch clamp recordings in acute GC slices to determine the effect of this form of learning on GC neuron excitability and the BLA-GC synapse. Our results indicate that CTA learning shifts the balance of excitatory and inhibitory synaptic inputs onto GC neurons toward excitation, and increases GC neuron intrinsic excitability. In addition, CTA learning weakens BLA-GC synapses, suggesting that CTA learning may depend on Long Term Depression (LTD) of the BLA-GC synapse and increased excitability of the GC circuit. To test this possibility, we first identified patterns of activity for LTD at BLA-GC synapses in slice preparations and tested whether CTA learning altered the capacity for this form of plasticity. In CTA trained animals, induction of LTD with a phasic activity paradigm was impaired and a competing Long Term Potentiation (LTP) was unveiled (% of neurons: Control - LTD, 63.3%; CTA - LTP, 58.8%; $\chi^2$, $p < 10^{-3}$), indicating that CTA learning has altered the state of BLA-GC synapses. This switch in the sign of plasticity was selective for the phasic induction paradigm, as tonic activation of BLA afferents induced

comparable LTD in control and CTA animals (Control - LTD, 91.7%; CTA - LTD, 100%). Finally, we asked whether phasic-LTD was sufficient to induce CTA. To do that, we substituted the gastric malaise typically paired with sucrose during CTA training with the phasic stimulation paradigm for LTD using optogenetic activation of BLA terminal fields in GC, and assessed CTA learning in rats. The pairing of sucrose and phasic-LTD activation of BLA afferents in GC was sufficient to induce a CTA. Our results demonstrate that CTA learning induces pleiotropic effects on GC circuits, and directly link CTA learning with LTD of BLA-GC synapses onto L2/3 EXC neurons.

**Disclosures:** **M. Haley:** None. **A. Fontanini:** None. **A. Maffei:** None.

**Poster**

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Cnpq

CAPES

AFIP

**Title:** Hubs involved in hipocampal loss compensation in contextual fear learning impair contextual discrimination

**Authors: *T. B. DOS SANTOS**, C. A. COELHO, M. G. M. OLIVEIRA
Univ. Federal De São Paulo, Sao Paulo, Brazil

**Abstract:** Pre-training dorsal hippocampus (dHPC) lesions do not impair contextual fear conditioning (CFC), suggesting that other structures can compensate and promote CFC learning. A previous study from our laboratory pointed to the perirhinal (PER) and retrosplenial cortices (RSC) as hubs in the network engaged in CFC learning in the absence of the dHPC. Current theories propose that the hippocampus forms a configural representation of the context, however, the contribution of these compensating hubs, and their interaction with dHPC, to a configural representation of the context are unknown. Here we employed double lesions to investigate the effect of pre-training double NMDA-induced lesion in dHPC and PER or dHPC and RSC on the performance of a contextual discrimination task. Male *Wistar* rats underwent neurotoxic lesions

in the dHPC, PER, dHPC+PER or were SHAM animals in experiment 1 (n = 11-12) or in the dHPC, RSC, dHPC+RSC or were SHAM animals in experiment 2 (n = 4-5). Contextual discrimination task consisted of 11 consecutive days in both experiments. First, animals were habituated for 5min in two different conditioning chambers that shared some contextual cues. In the next nine days, one chamber was designated as the shock-Context (CT+) and other as the no-shock Context (CT-), in a counterbalanced manner. When placed in CT+, rats received a footshock (0.8mA, 1s) after 4min and then were removed after 1min. When placed in CT-, rats were allowed to explore it for 5min and no footshock was delivered. Rats were exposed to one of the contexts in the morning and the other in the afternoon (counterbalanced). On the 11$^{th}$ day, animals were exposed to CT+ and a third context (CTn), totally different from CT+ and CT-, for 4min. Freezing time was measured during all sessions as a fear memory index. Multivariate Analysis of Variance (corrected for multiple comparisons) showed that both SHAM and dHPC+PER groups discriminated between the Contexts from block 2, but the groups with individual lesions of dHPC or PER did not discriminate. In experiment 2, both RSC and dHPC+RSC groups showed a tendency of impairment of the contextual discrimination task. The present results suggest that both PER and RSC are important for a configural representation of the context, but their interaction with dHPC is not trivial. Paradigms that evaluate acquisition of multiple levels of information complexity could better dissect these regions contribution in context representation.

**Disclosures:** **T.B. Dos Santos:** None. **C.A. Coelho:** None. **M.G.M. Oliveira:** None.

**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

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Brain and Behavior Foundation NARSAD award

**Title:** microRNA regulation of traumatic memory storage

**Authors: *S. SILLIVAN**, N. JOSEPH, S. JAMIESON, C. MILLER
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**Abstract:** Understanding how the brain maintains a stable memory for months to years has significant implications for disorders perpetuated by pathogenic memory, such as post-traumatic stress disorder (PTSD). Despite the clinical importance of memory storage, mechanisms of long-lasting memory are understudied and elusive. Previously we identified microRNA (miRNA) changes in the amygdala (AMY) that persist a month after learning, suggesting that miRNAs may be key participants in long-term memory storage. Given that a single miRNA has hundreds of predicted targets, their wide-genomic range has the complexity to maintain a lasting "traumatic" memory, which has relevance to PTSD. We recently developed a preclinical PTSD model that employs stress enhanced fear learning (SEFL) by combining an acute stressor with Pavlovian fear conditioning (FC) to recapitulate many hallmark features of PTSD in an inbred mouse strain, including differential vulnerability to stress. The stress susceptible (SS) subpopulation displays persistently elevated, extinction-resistant fear memory. Importantly, we identified a relationship between SEFL behavior and extinction performance to predict SS and stress-resilient (SR) animals. This eliminates a confound of additional behavioral phenotyping and allows for study of the underlying molecular mechanisms, including miRNAs. We used this model to investigate the 'miRNAome' associated with a perseverant "PSTD-like" memory by performing small RNA sequencing (miRNA-Seq) to measure lasting miRNA expression (>30 days) in the AMY after SEFL. 123 miRNAs were differentially expressed between SS and SR animals and 164 between SS and FC animals, with most miRNAs upregulated in SS relative to SR or FC. Only 71 were different between FC and SR, indicating that SR animals are more like FC than SS animals. We then performed quantitative mass spectrometry to identify the proteomic profile of the AMY in SEFL animals and aligned it with the miRNA-Seq data. A general downregulation of proteins was observed in SS mice, relative to SR or FC only, and the proteomic profile of SS vs SR was similar to SS vs FC only mice. The global increase in miRNA levels but decrease in protein levels in SS mice suggests unique miRNA-mediated translational pathways may be recruited for traumatic memory storage. We are currently testing the functional impact of *in vivo* manipulation of candidate miRNA pathways on the maintenance of a 30 day-old PTSD-like memory. Identification of miRNAs participating in the storage of traumatic memory will provide clear targets for selective and immediate disruption of the memory, which has significant therapeutic implications for conditions like PTSD.

**Disclosures: S. Sillivan:** None. **N. Joseph:** None. **S. Jamieson:** None. **C. Miller:** None.

**Poster**

**513. Fear and Aversive Learning and Memory: Neural Circuits II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 513.16/RR25

**Topic:** G.01. Appetitive and Aversive Learning

**Support:** German Research Foundation (DFG; SFB-TR58, TPA08 to K.J., TPA03 to H.-C.P.)

Cells in Motion International Max-Planck Research School (fellowship to L.G.)

Interdisciplinary Center for Clinical Research of the Medical Faculty Münster (IZKF Jün3/003/17)

**Title:** μ-opioid receptor-mediated attenuation of midline thalamic inputs to the amygdala

**Authors: *L. GOEDECKE**, P. BLAESSE, H.-C. PAPE, K. JÜNGLING
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**Abstract:** The dorsal midline thalamus (dMT) is implicated in the retrieval of fear memories. It is innervated by a vast array of neuropeptidergic fibers, containing e.g. enkephalin. Moreover, dMT neurons express μ-opioid receptors (MORs), suggesting a neuromodulatory role for the μ-opioid system in this region. Efferent projections of the dMT target a variety of subcortical structures that regulate emotional behavior, among them the basal (BA) and centrolateral (CeL) nucleus of the amygdala. Within the amygdala, BA sends excitatory projections to neurons of the centromedial amygdala (CeM), which mediates conditioned fear behavior via projections to brain stem and hypothalamic nuclei. The CeL, on the contrary, exerts inhibitory control over the CeM. While dMT-projections to the CeL have been shown to be required for fear memory retrieval, the role for dMT-BA synaptic connections is less clear. In order to electrophysiologically characterize dMT-BA and dMT-CeL synaptic connections and investigate how they are functionally modulated by MORs, we performed whole-cell patch clamp recordings in acute brain slices of mice in combination with retrograde tracing or optogenetics. Furthermore, *ex vivo* recordings were conducted to study whether cued fear memory retrieval is associated with changes in glutamatergic synaptic transmission at dMT-BA projections. We found that MORs mediate the hyperpolarization of both BA-projecting and CeL-projecting dMT neurons. In addition, we showed that both BA and CeL neurons receive excitatory input from dMT neurons and generate fast postsynaptic responses (eEPSCs). Activation of MORs attenuated transmission at both dMT-BA and dMT-CeL synapses and, furthermore, reduced dMT-driven feedforward excitation of CeM neurons. Interestingly, dMT-CeL and dMT-BA connections differed with regards to apparent synaptic connectivity, eEPSC amplitude, and modulatory influence of the MOR system. Moreover, preliminary results indicate that cued fear memory retrieval, indeed, affects glutamatergic transmission at dMT-BA syapses. Together, these results suggest that MORs are important negative modulators of synaptic transmission between dMT and amygdala, a circuit that is critically involved in the expression of emotional behaviors such as fear.

**Disclosures:** **L. Goedecke:** None. **P. Blaesse:** None. **H. Pape:** None. **K. Jüngling:** None.

**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 514.01/RR26

**Topic:** G.03. Emotion

**Support:** Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) Research Grant #2014/05432-9 to NSC

**Title:** Regional c-fos expression in rats confronted by a non-coevolved predator

**Authors: *D. C. BLANCHARD**[1,2], S. C. MOTTA[3], M. V. C. BALDO[3], J. M. TESSARI[4], N. C. COIMBRA[4], N. S. CANTERAS[3]
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**Abstract:** Anxiety and the depressive disorders with which anxiety is frequently comorbid constitute an enormous illness burden in the US and elsewhere. Detailed analyses of response to threat in laboratory rodents suggest that a particular defensive behavior, risk assessment (RA), is prominent in response to potential, rather than clear, threat. Functionally, RA is related to rumination and eye-gaze movement behaviors, both of which have been shown to be aberrant in anxious and depressed individuals, suggesting that it may have potential as a transdiagnostic preclinical model.
Snakes of non-coevolved species provide a model whose threat properties are more ambiguous than are those of coevolved predators. Snakes of species native to South America have been isolated from species such as R. norvegicus, evolving in central Asia, for over 50 million years. Rats confronted by two species of South American snakes showed much higher levels of RA and fewer flight or freezing defenses than those typically seen in encounters with coevolving predator species such as cats: Moreover, as predicted from previous analyses, levels of each type of defensive behavior varied with the activity and directed attack behaviors shown by the snakes. Activity in the rat subjects' brains was evaluated by regional tallies of cells showing expression of the intermediate early gene, c-fos, in 37 different regions of interest (ROIs), including those that have previously been linked to defensive behavior. Regional subcortical activity patterns were similar but not identical to those found in cat encounters, with particular differences found in the ventromedial nuclei of the hypothalamus. Although overall levels of defensiveness, based on instances or durations of a range of defensive behaviors, correlated highly with fos counts in some ROIs, counts in other ROIs suggested differential associations with RA, freezing, and flight. This model may prove particularly interesting in analysis of cognitive aspects of defensiveness, with enhanced relevance to anxiety and anxious depression.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 514.02/RR27

**Topic:** G.03. Emotion

**Support:** R01 MH099073

**Title:** A novel naturalistic paradigm to study aerial predatory-induced fear in laboratory rats

**Authors:** ***P. R. ZAMBETTI**[1], E. KIM[1], J. J. KIM[1,2]
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**Abstract:** Despite the breadth of risky situations in nature that demand diversity in fear behaviors, contemporary neurobiological models of fear are based largely on Pavlovian fear conditioning studies that focus on how a particular cue upon pairing with an aversive (usually painful) event becomes capable of eliciting learned fear responses. Ecological studies, however, have maintained that innate fear to sudden stimuli (evolutionarily reliable signals of threat) is vital to guide and shape adaptive behaviors because unlearned fear would provide a competitive advantage over the time-consuming and hazardous process of trial-and-error fear learning (see Pellman and Kim, 2016). One popular innate fear paradigm in rodents (usually mice) employs looming overhead stimuli through either an expanding disc or sweeping bar, to which animals instinctively display freezing and/or flight behaviors in small testing chambers. It has been proposed (Fanselow and Lester, 1988) that rodents would freeze to distal predators to avoid detection, but switch to fleeing to proximal predators, as freezing would be maladaptive. To investigate the dynamics of defensive behaviors in rats, we employed a realistic owl replica that plunges towards animals foraging for food in a large arena. In response to this predatory model, all rats instinctively fled to and froze inside the safe nest area, and no freezing was observed out in the arena. Our aerial predatory paradigm will be useful for investigating how the brain processes and responds to different (i.e., terrestrial vs. aerial) predatory threats.

**Disclosures:** **P.R. Zambetti:** None. **E. Kim:** None. **J.J. Kim:** None.

**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 514.03/RR28

**Topic:** G.03. Emotion

**Title:** A robot dinosaur as a predator like stressor to highlight susceptibility versus resilience and gender difference in response to acute stress

**Authors: *A. MENIGOZ**[1], C. BATTERMAN[2], D. G. RAINNIE[2]
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**Abstract:** It is clear that stress affects emotional behavior, however each individual responds differently to adversity. Many resilient individuals display adaptive physiological responses to stress while others will develop depression or other psychiatric disorders. Moreover, there is an overwhelming wealth of evidence from the clinical literature that the prevalence of anxiety disorders is about twice as high in women compared to men. The molecular pathways underlying these differences remain unclear. Here, we used a new stressor, a robotic predator, in a 3 day paradigm (Baseline, Stress and Probe test), to induce acute stress in males (n=14) and females rats (n=12). The time spent interacting with the predator was used to assess the stress response. In males, we found that the interaction time significantly decreased during Stress compared to Baseline (18.28% vs 35.44% $p<0.001$ RM-ANOVA). Interestingly, during Probe about 71% of the males still displayed reduced interaction while 29% showed no difference compared to their Baseline behavior. We could not find a specific behavior during the Stress that could be correlated with the stress response during Probe, suggesting an endogenous component to the resilience. Unexpectedly, in females, a significant proportion of the animals did not display sign of stress in response to the moving predator while about 40% significantly decreased their interaction. Females with decreased interaction during Stress also showed decreased interaction during Probe while resilient animals during Stress displayed normal behavior during probe. We found a significant correlation between the behavior during Stress and Probe (Spearman $r=0.7852$). Previous studies have reported that the light-enhanced startle response in female rats fluctuated significantly with reproductive state. We hypothesized that the fluctuation we observed in response to the stressor might be the result of different estrogen and estrogen receptor levels.
In both males and females, we then investigated the neuronal activation in response to the presentation of the stressor on D2 and D3 as well as the level of estrogen and estrogen receptors and blood cortisol. After identification of the responding neurons, we will use the TRAP technology to characterize their transcriptomic profile and potentially highlight genes involved in stress resilience.

**Disclosures:** **A. Menigoz:** None. **C. Batterman:** None. **D.G. Rainnie:** None.

**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

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**Program#/Poster#:** 514.04/RR29

**Topic:** G.03. Emotion

**Support:** NIH grant 5R01MH072908-12

**Title:** Stress neuroadaptation in the bed nucleus of the stria terminalis (bnst) may underlie social defeat-induced depression-related behaviors

**Authors: *S. E. HAYNES**[1,2], A. MENIGOZ[2], C. BATTERMAN[2], D. G. RAINNIE[3]
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**Abstract:** Chronic stress is a key risk factor in the development of Major Depressive Disorder (MDD), yet it is unknown why certain people develop MDD compared with others, despite reporting similar levels of stress. Corticotrophin-Releasing Factor (CRF) has emerged as a molecular substrate that may play a critical role in stress-related depression. Although, CRF's potential role is implicated in a preponderance of preclinical and clinical reports, how stress and CRF play a pivotal role in MDD etiology is not well understood. The Bed Nucleus of the Stria Terminalis (BNST) may be in important in the interrelationship of stress and depression, as it encodes the nature and chronicity of stressful stimuli and mediates behavioral/physiological adaptive responses. Importantly, the oval nucleus of the BNST contains an enriched population of CRF postitive ($BNSTov^{CRF}$) neurons that are stress responsive and serve as an attractive neuronal population to interrogate as providing a molecular link between CRF and depression. In this study, we sought to elucidate CRF neural mechanisms that underlie individual differences in stress susceptibility that arise from unmitigated chronic stress exposure. We hypothesized that individual differences in crf gene expression may correlate with an individual's vulnerability to depression. To test this, we employed the Chronic Social Defeat Stress paradigm in mice that reliably produces stress-resilient (RES) or depressive-like (DEP) phenotypes on the basis of social interaction and sucrose preference. We discovered differential *crf, crfr1,* and *crfr2* gene expression in the anterolateral (oval nucleus containing) region of the BNST of RES and DEP mice. Additionally, these changes in gene expression correlated with immediate early gene, *cfos,* activity selectively in the BNSTov, but not anteromedial or ventral BNST regions. Notably, we observed in crf-tdTomato mice, the co-localization of cfos immunofluorescence with tdTomato, suggesting these changes may be mediated by this CRF-positive neuronal subpopulation. Altogether, these findings provide evidence that the response of BNSTov CRF neurons to

persistent stress may reflect individual tolerance to stress such that hypoactivity may predispose individuals to depression. Alterations in CRF neurotransmission may shift the predisposition of mice toward either stress-resiliency (RES) or stress-induced depressive-like (DEP) phenotypes. In this way, CRF transmission in the BNST may serve as a biomarker in serving to identify populations of individuals with enhanced vulnerability to depression.

**Disclosures: S.E. Haynes:** None. **A. Menigoz:** None. **C. Batterman:** None. **D.G. Rainnie:** None.

**Poster**

**514. Circuits Underlying Emotional States**

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**Topic:** G.03. Emotion

**Support:** NIH Grant MH105427

NIH Grant NS078434

**Title:** Genetically modified rabies tracing of global circuit connections to corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus

**Authors: *X. XU**[1], P. RIGAS[2], Y. SUN[1], C. A. ITOGA[1], K. LAM[1], J. D. DELGADO[1], E. M. CALLAWAY[3], E. KIM[4]
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**Abstract:** Corticotropin-releasing hormone (CRH)-containing neurons in the paraventricular nucleus (PVN) of the hypothalamus play a key role in the hypothalamic-pituitary-adrenal (HPA) axis stress responses. The existing knowledge about PVN circuit connections comes from conventional anatomical studies which tend to have low spatial and cell type resolution. Many aspects of neural circuit organization of CRH+ PVN neurons are poorly understood. Thus we have mapped global synaptic connections to these CRH+ neurons in order to better understand how they integrate stress-relevant signals from brain-wide neural networks to regulate the neuroendocrine response to stress. A new Cre dependent monosynaptic rabies tracing system with the helper AAV expressing optimized glycoprotein (oG) was used to map direct circuit connections to CRH+ neurons in the PVN of CRH-ires-Cre mice. Reproducible results of synaptic input patterns were obtained from 6 high quality cases. We found that these CRH neurons received synaptic connections from more than one hundred brain regions. Hypothalamic regions account for the majority of inputs, as dorsomedial, ventromedial, lateral hypothalamus, lateral and medial preoptic nucleus, and the arcuate nucleus have on average, 11.5%, 10.9%,

8.1%, 17%, and 18% of total labeled presynaptic neurons, respectively. While there are no or little direct inputs from sensory and motor cortex, hippocampus or amygdalar nuclei, there are readily identifiable inputs from infralimbic cortex (0.4% of total labeled presynaptic neurons), the nucleus accumbens (2.8%), anteromedial and ventral thalamus (0.9%), lateral and medial septum (4%), dorsal and ventral subregions of the bed nucleus of the stria terminalis (3.3%), supraoptic nucleus (0.26%), zona incerta (0.7%), periaqueductal gray area (0.9%), periventricular nucleus (0.6%), and mammillary nuclei (0.6%). Antibody immunostaining was used to further identify the excitatory or inhibitory nature of input mapped neurons. All these regions, including previously un-described input sources, have been significantly implicated in emotion, reward and / or stress regulation. Our work aided by the new viral genetic mapping approach, allows for a detailed analysis of global information flow directly impinged on CRH+ PVN neurons and will shed new light on specific neural circuit mechanisms underlying direct control of HPA axis responses.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 514.06/RR31

**Topic:** G.03. Emotion

**Support:** HCIA

**Title:** Functional dissection of the dorsal raphe serotonin systems

**Authors:** ***J. REN**[1], D. FRIEDMANN[1], J. XIONG[2], C. LIU[1], K. E. DELOACH[2], R. L. NEVE[3], C. RAN[1], A. PU[4], M. HOROWITZ[2], L. LUO[1,5]
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**Abstract:** The serotonin system powerfully modulates physiology and behavior in health and disease. The major source of serotonergic innervation of the forebrain originates from the dorsal raphe nucleus (DR). Most previous studies of serotonin regulation of physiology and behavior treat the DR serotonin system as a single entity. Our recent whole-brain mapping of monosynaptic inputs to DR suggested heterogeneity of serotonin neurons with respect to input they receive (Weissbourd et al., *Neuron* 83:645-662, 2014). We now report that retrograde tracing from 8 distinct brain area revealed that serotonin neurons project to specific output sites have a stereotyped cell body locations in the DR. For example, serotonin neurons that project to olfactory bulb and cortical areas such as prefrontal cortex (PFC) and entorhinal cortex are

concentrated in the ventral DR. By contrast, serotonin neurons that project to subcortical areas, such as central amygdala (CeA), thalamus, hypothalamus, tend to distribute in the dorsal DR. Collectively, these data suggest that the DR serotonin neurons consist of parallel sub-systems. We next selected DR serotonin neurons that project to PFC and CeA as two representative sub-systems for further investigation. By combining retrograde viral tracing and iDISCO+-based brain clearance method, we found that PFC- and CeA-projecting DR serotonin neurons have specific collateralization patterns that are largely non-overlapping. We further used cTRIO method we recently established (Schwarz et al., *Nature* 524:88-92) to map the input-output relationship, finding that PFC-projecting DR serotonin neurons have biased input from lateral hypothalamus and medulla, whereas CeA-projecting ones receive stronger input from CeA itself and from the bed nucleus of the stria terminalis. We are currently using fiber photometry and chemogenetics to record and manipulate the activity of these two groups of neurons in behavioral paradigms that may be regulated by serotonin. Together, these experiments begin to decompose the DR serotonin system into distinct sub-systems, each of which likely has unique anatomical, physiological, and functional properties.

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**Poster**

**514. Circuits Underlying Emotional States**

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**Topic:** G.03. Emotion

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ANR–10–LABX–54 MEMOLIFE

ANR–10–IDEX–0001–02 PSL* Research University

**Title:** Cerebellar involvement in brain emotional circuits

**Authors: *J. L. FRONTERA**[1,2], C. MAILHES-HAMON[2], D. POPA[2]
[1]Inst. De Biologie De L'Ens, Paris, France; [2]Dept. de Biologie, Inst. de Biologie de l'Ecole Normale Supérieure, Paris, France

**Abstract:** Fear conditioning is a form of learning that serves as model to study the neurobiological basis of disorders of fear and anxiety. Available data suggest that pathological forms of anxiety result from a deficit in the acquisition, expression or extinction of the emotional responses. The role of brain structures such as the amygdala and the prefrontal cortex in these

phenomena is well established, but recent data indicate an involvement of the cerebellum in emotional disorders. Using a combination of neuroanatomy, behavior, and pharmacogenetics approaches, we are studying the cerebellum and the limbic forebrain circuit in fear conditioning in mice.
We mapped the cells in the amygdala responding to cerebellar stimulations followed by immunolabeling of the early gene Zif/268 to identify neurons activated by the cerebellar stimulation in mice expressiong ChannelRhodopsin in Purkinje cells, L7ChR and we found clusters of labeled cells in the basolateral and central nuclei of the amygdala contralateral to the stimulation.
We also mapped the brain pathways linking the cerebellum to the limbic system using different retrograde markers (Cholera Toxin subunit B-alexa 555, -alexa 488, -CF594) injected in the prefrontal cortex and the amygdala, and anterograde virus (AAV1.CB7.Cl.mCherry.WPRE.rBG) injected in the cerebellar nuclei. We found multiple putative thalamic relays where the fibers from fastigial nucleus as well as somas of neurons projecting to prefrontal areas and amygdala converged. We transiently silenced the neuronal activity of cerebello-thalamic pathway during fear conditioning using pharmacogenetics and we found cerebellar modulation on fear memory consolidation, suggesting that the cerebellum is engaged in the limbic forebrain function and in the processes that take place in fear learning and extinction.

**Disclosures:** **J.L. Frontera:** None. **C. Mailhes-Hamon:** None. **D. Popa:** None.

**Poster**

**514. Circuits Underlying Emotional States**

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**Program#/Poster#:** 514.08/RR33

**Topic:** G.03. Emotion

**Support:** DA035371

DA041482

**Title:** Mesointerpeduncular circuitry and dopaminergic control of affective state

**Authors: *S. R. DEGROOT**, R. ZHAO-SHEA, P. D. GARDNER, A. R. TAPPER
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**Abstract:** Anxiety disorders are the most common class of mental disorders. Anxiety is an affective state classically governed by the prefrontal cortex, hippocampus, and the extended amygdala, which includes the bed nucleus of the stria terminalis (BNST). Previous studies suggest that stimulation of glutamatergic BNST efferents in the ventral tegmental area (VTA) is anxiogenic. Further, the VTA can exhibit control of affective state by heterogeneous efferent

terminal activation in certain brain regions. Recently, we showed that the mesointerpeduncular circuit, which consists of VTA dopaminergic (DAergic) neurons that innervate the interpeduncular nucleus (IPN), is an important component in nicotine withdrawal-induced anxiety. The current study further explores the mesointerpeduncular circuitry, specifically DAergic control of the IPN in drug naïve mice. Using cell-attached patch-clamp electrophysiology in acute mouse midbrain slices, we defined two neuronal populations of the ventral IPN by input resistance and response to exogenous application of DA. “Type A” neurons displayed low input resistance and responded to DA with an increase in spontaneous action potential frequency (sAPF), while “Type B” neurons exhibited a higher input resistance and responded to DA with a decrease in sAPF. Whole-cell patch clamp recordings revealed changes in excitatory postsynaptic current frequency, but not amplitude in IPN neurons during VTA terminal stimulation suggesting that DA acts presynaptically to modulate IPN inputs Using viral mediated gene delivery and CRE-Lox technology, we expressed channelrhodopsin-2 (ChR2) specifically in putative DAergic VTA neurons of DA transporter (DAT)-CRE mice. Optogenetic stimulation of VTA neurons resulted in changes in sAPF prominently in the caudal IPN. These responses were blocked by D1-family DA receptor (DRD1) antagonists and were localized to the area where putative DRD1-expressing cell bodies were detected. Dopaminoceptive caudle IPN neurons exhibited significantly higher input resistance compared to Type A or B neurons suggesting a third neuronal subtype, “Type C”. Optogenetic stimulation of putative DRD1-expressing Type C neurons in the IPN of DRD1-Cre mice resulted in responses of ventral IPN Type A and Type B neurons that phenocopied the response to exogenous DA application. Together, our results identify a novel microcircuit by which the VTA controls activity of the IPN to potentially modulate affective behavior.

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**Poster**

**514. Circuits Underlying Emotional States**

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**Program#/Poster#:** 514.09/RR34

**Topic:** G.03. Emotion

**Support:** NIH Intramural Funding

**Title:** Cortical neural correlates of major depressive disorder

**Authors: *A. VAZ**[1], A. H. TIPPUR[2], S. K. INATI[3], K. A. ZAGHLOUL[4]
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**Abstract:** Recent reports have shown subcortical neural correlates of psychiatric disorders such as depression and obsessive compulsive disorder. However, investigations to date have mostly consisted of recordings made in brain stimulation paradigms with relatively limited spatial resolution and only in specific clinical scenarios. Additionally, intracranial recording electrodes are generally not indicated for the management of psychiatric disorders, and thus these pathologies are poorly studied in terms of cortical electrophysiology. Here we use cortical surface intracranial EEG (iEEG) recordings in epilepsy patients being monitored for seizure localization to identify cortical neural correlates of major depressive disorder (MDD). Our classification of MDD was predicated upon a clinical diagnosis and reaffirmed with the Beck Depression Index version 2. When comparing across all participants, we found neural correlates of MDD in the left temporal lobe. In particular, we observed significantly lower broadband spectral power in patients identified with MDD, and importantly, it appears that these markers were independent of any seizure activity. These data suggest that dysfunctional cortical mechanisms may contribute to MDD and that further investigation is warranted to elucidate diagnostic and therapeutic approaches to psychiatric disorders in humans.

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**Poster**

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Deutsche Forschungsgemeinschaft SCHU 2471/5-1

Neuropsychoanalysis Foundation Grant

**Title:** Cardiac interoceptive inference: Evidence from heart-beat evoked potentials

**Authors: *A. SEL**[1], A. GENTSCH[2], S. SCHÜTZ-BOSBACH[2], M. TSAKIRIS[3]
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**Abstract:** The ability to perceive internal bodily states such as hunger, thirst, pain, muscular and visceral sensations, known as interoception, is regarded as a fundamental basis for emotional processing and (embodied) selfhood. For many years, interoception was regarded as a purely bottom-up, sensory-driven phenomenon, based on the representation of afferent sensory input from the body. However, recent accounts suggest that interoception is a top-down, prediction-

driven phenomenon that, as with other sensory modalities, enables the inference of the causes of bodily sensations on the basis of past experiences. In this EEG study we tested this hypothesis investigating the neural responses to heartbeats following expected and unexpected emotional stimuli. We used a modified stimulus repetition task while measuring evoked cortical responses from 17 human participants. During the task, participants observed pairs of facial expressions presented with repeating or alternating emotional content. We manipulated the emotional valence and the likelihood of stimulus repetition. The results of the study showed that the heartbeat-evoked potential, a marker of cardiac interoception, was increased for repeated (and thus, expected) neutral faces, whereas the opposite was observed for negative faces. Our results are in line with recent models of interoceptive predictive coding and help to elucidate the role of emotion in predictive processing underlying interoception. In particular, these results suggest that cardiac interoceptive responses are enhanced when processing an expected, compared with an unexpected, neutral emotional event. In contrast, for negative emotional events, successful top-down prediction appears to result in reduced interoceptive processing and thus, reduced embodied self-awareness.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

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**Topic:** G.03. Emotion

**Support:** Wellcome Trust Investigator Award 108089/Z/15/Z to A.C.R.

MRC studentship to L.A.

MRC Career Development Award RG62920 to H.F.C.

**Title:** Transient anticipatory anhedonia induced by over-activation of primate subgenual cingulate is reversed by ketamine

**Authors: *L. ALEXANDER**[1], H. F. CLARKE[1], S. J. SAWIAK[2], T. D. FRYER[2], Y. T. HONG[2], A. C. ROBERTS[1]
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**Abstract:** Anhedonia is a core symptom of depression, but the underlying neurobiological mechanisms remain unclear. Correlative neuroimaging studies implicate dysfunction within the highly heterogeneous ventromedial prefrontal cortex, but the causal role of specific subregions is unknown. We addressed these issues by combining intracerebral microinfusions with

cardiovascular and behavioral monitoring in marmoset monkeys to show for the first time that pharmacological over-activation of primate subgenual anterior cingulate cortex (sgACC, area 25) causes anticipatory but not consummatory anhedonia, whereas neither over-activation nor inactivation of perigenual ACC (pgACC, area 32) has any effect. The anhedonia induced by sgACC/25 over-activation was replicated using chemogenetic excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), enabling us to localize the source of this anticipatory deficit to over-activity in pyramidal output neurons within sgACC/25. These same chemogenetic manipulations had no effect on sucrose preference in the sucrose consumption test, a common measure of consummatory anhedonia used in rodent studies. We subsequently demonstrated that the anticipatory anhedonic deficit could be ameliorated with ketamine in a time-dependent manner. $^{18}$F-FDG microPET imaging revealed that over-activity in dorsal ACC and anterior insula accompanied the anhedonia induced by sgACC/25 over-activation, changes which were all reversed by ketamine. These results demonstrate a causal role for sgACC/25 over-activity in anhedonia, and ketamine's modulation of an affective network to exert its action.

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**Poster**

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**Program#/Poster#:** 514.12/SS1

**Topic:** G.03. Emotion

**Support:** DARPA Cooperative Agreement Number W911NF-14-2-0045

**Title:** Cingulate stimulation bidirectionally changes emotion regulation during an emotion conflict resolution task

**Authors: *A. C. PAULK**[1], K. FARNES[1], A. YOUSEFI[5], M. M. ROBERTSON[2], D. VALLEJO-LOPEZ[3], S. ZOROWITZ[4], B. CROCKER[6], N. PELED[7], K. ELLARD[8], T. DECKERSBACH[8], D. DOUGHERTY[8], A. S. WIDGE[4], E. N. ESKANDAR[1], S. S. CASH[9]
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**Abstract:** Individuals must be able to integrate complex, even conflicting, emotional signals to regulate their emotions depending on their relevance to current, ongoing contextual demands.

Insufficiencies in this type of emotion regulation have been demonstrated across many psychiatric disorders. We made use of intracranial recordings in participants with epilepsy to define the regions and types of neural activity that subserve emotion regulation as elicited in the Emotional Conflict Resolution (ECR) task. The ECR task consistently induced significant widespread activation of the brain across participants (N=15). In addition, we found that ECR task-relevant behavior is significantly correlated to the LFP voltage and theta (4-8 Hz) and high gamma (65-200 Hz) power signal in brain regions predicted by imaging studies, such as the dorsal anterior cingulate cortex (dACC), amygdala, and the rostral anterior cingulate cortex (rACC). Targeting these same regions using high frequency focal neural stimulation, we altered participant behavior bidirectionally depending on which brain regions were stimulated. We then used these results to introduce closed-loop stimulation, such that the ongoing behavior on a trial to trial basis was used to trigger electrical stimulation of brain regions. We found we could alter behavior in closed loop fashion in a participant performing ECR. These results not only support fMRI literature demonstrating the importance of the salience networks' involvement in emotion regulation, but illustrate that neural stimulation in this network can alter behavior and, thus, may eventually provide a therapeutic modality for people suffering from emotion dysregulation.

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**Poster**

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**Program#/Poster#:** 514.13/SS2

**Topic:** G.03. Emotion

**Support:** DARPA Cooperative Agreement Number W911NF-14-2-0045

**Title:** Cognitive networks are activated to compensate for emotion dysregulation during emotion versus cognitive conflict tasks

**Authors: K. FARNES**[1], M. M. ROBERTSON[2], A. C. PAULK[1], *I. BASU[3], A. YOUSEFI[6], D. I. VALLEJO[7], S. ZOROWITZ[4], A. AFZAL[5], N. PELED[8], N. NOSSENSON[9], K. ELLARD[5], T. DECKERSBACH[5], D. DOUGHERTY[5], E. N. ESKANDAR[1], A. S. WIDGE[4], S. S. CASH[10]
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**Abstract:** How humans respond to emotional stimuli in the face of conflict is influenced by how emotions are regulated internally while responding to emotional stimuli. This can contrast with how humans respond to conflict without emotional stimuli, such as in cognitive tasks. Difficulties with regulating emotion or resolving cognitive conflict have been demonstrated across many psychiatric disorders. Understanding this complex, and highly integrated, process requires we understand neural activity dynamics as individuals switch between non-emotional and emotional tasks. We chose to compare neural activity during the Emotion Conflict Resolution (ECR) task and the Multi-Source Interference Task (MSIT). We wanted to identify the neural correlates of behavior that are either unique or intersectional between MSIT and ECR, particularly in light of whether the underlying state of emotion reactivity, as measured by self-report questionnaires, alters these dynamics. Our findings from intracranial recordings of patients with intractable epilepsy (N=15) align with previous fMRI imaging literature. We were also able to confirm the activation of cortical structures involved in resolving non-emotional conflict by inspecting the size of voltage deflections and changes in theta band (4-8 Hz) power. Lateral pre-frontal cortex (PFC) and dorsal anterior cingulate cortex (dACC) had significant theta band power changes during both tasks ($p<0.05$, fdr corrected t-test). During the resolution of emotional conflict, there was additional activation of dorsal medial PFC and subcortical structures, amygdala and rostral anterior cingulate cortex (rACC). Several of these regions also had changes in high gamma power (65-100Hz) when resolving conflict. There was a significant increase ($p<0.05$, Wilcoxon rank sum) in network connectivity, as measured by theta band coherence, between lateral PFC and other cortical structures during MSIT relative to ECR. During ECR, connectivity increased between rACC and dACC. However, this was only the case for participants with low emotional reactivity, as measured with their questionnaire responses. Those with high emotional reactivity had coherence changes during ECR that were similar to those occurring during MSIT, albeit with smaller magnitude. We interpret this to mean that participants with high emotional reactivity do not utilize the same networks to resolve emotional conflict to perform ECR, instead relying heavily on the networks required to solve non-emotional, or cognitive, conflict. Activating emotional conflict resolution networks may be a therapeutic route for those struggling with emotion dysregulation.

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**Poster**

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**Program#/Poster#:** 514.14/SS3

**Topic:** G.03. Emotion

**Support:** DARPA Cooperative Agreement Number W911NF-14-2-0045

**Title:** The nonlinear relationship between stimulation frequency, amplitude and local responses in cortical and subcortical regions of the human and non-human primate brain

**Authors: *M. M. ROBERTSON**[1,2], I. BASU[2], A. C. PAULK[2], K. FARNES[2], D. I. VALLEJO[3], B. CROCKER[5], D. D. DOUGHERTY[4], E. N. ESKANDAR[2], A. S. WIDGE[4], S. S. CASH[3]
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**Abstract:** Recent studies have found success in treating refractory neuropsychiatric disorders through neural stimulation. While actively employed to treat several disorders, including epilepsy and Parkinson's disease, knowledge is sparse regarding the way in which stimulation parameters such as frequency and amplitude influence changes in neural activity. We examine the functional relationship between pulse frequency and current amplitude during short trains of stimulation ranging from 10-200 Hz by evaluating the evoked response in cortical and subcortical brain regions adjacent to sites of stimulation in both human (N= 6) and non-human primates (NHP, N=3). Specifically, we evaluate the evoked response in the amygdala, and the dorsal and rostral anterior cingulate cortices (dACC, rACC) of human participants undergoing invasive monitoring for resective epilepsy surgery, and in the rACC, dACC, and the nucleus accumbens (NAcc) of NHPs chronically implanted with depth electrodes. These methods allow us to better understand the stimulus space for inducing targeted changes in neural activity in brain regions that have been associated with neuropsychiatric disorders, including depression, post-traumatic stress disorder, and addiction. We found that in both humans and NHPs, the peak evoked potential voltage response and the delay of the peak response increases until reaching a stimulation frequency between 90 and 130 Hz, and then either saturates or decreases as we step up to higher stimulation amplitudes and frequencies. Thus, stimulation frequency and current amplitude have a non-linear relationship with the peak response and the delay of this peak response. This non-linear mapping also depends on the brain region being stimulated, particularly in terms of subcortical and cortical targets. Similarly, neither stimulation amplitude nor frequency alone adequately predicted evoked changes in power. Instead, the interaction between stimulation amplitude, frequency, and recording location was important in producing a significant evoked change in power. These results suggest that there exists a set of amplitude and frequency parameters that will result in the highest local evoked responses to short trains of

stimulation at any specific brain region. This information begins to provide the basis for a principled selection of stimulation parameters to achieve maximal therapeutic benefit.

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**Poster**

**514. Circuits Underlying Emotional States**

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**Title:** Decoding task states from distributed local field potential recordings

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**Abstract:** The brain is a distributed network that operates at small and large spatial and temporal scales to meet the needs of the task at hand. Certain tasks generate conflict by requiring attention to relevant stimuli among distractions. Engagement in conflict-based tasks elicits network activity that differentiates these tasks from other behaviors. Brain states associated with conflict in experimental behavioral contexts may be an important marker of dysfunction related to mental illness, yet there are no documented decoders that predict engagement in conflict-based tasks through invasive, large scale local field potential recordings. In addition, there is evidence that precisely timed deep brain stimulation (DBS) could restore normal task behavior in neuropsychiatric patients; however, these findings are limited to within task features. In the present study, we have developed a decoding strategy to accurately predict task engagement by harnessing canonical correlation analysis (CCA), a measure of functional connectivity between regions, in tandem with a support vector machine (SVM) classifier. Cortical and sub-cortical invasive local field potential recordings were collected from patients engaged in one of two

Stroop-like tasks: the multi-source interference task (MSIT) or the emotional conflict resolution task (ECR). Canonical correlation coefficients were extracted by performing singular value decompositions on windows of data across all channels within each region and transforming the resulting singular vectors in a way that maximally correlates activity between each region pair. These CCA features were used as inputs to an SVM classifier to differentiate functional connectivity between task engagement and free behavior. A mean classification accuracy greater than 95% was achieved for both tasks across 14 patients and a subset of features per patient required to maintain high accuracy were isolated. The reduced feature set can be used to reduce the computational complexities of the algorithm moving forward, which points to potential tractability for driving a simple algorithm to detect task engagement on existing systems. While decoder stability was not achieved over two recordings, classification accuracy improved when trained on both recordings. This increase in accuracy suggests that training the classifier on many temporally separated datasets could improve its stability. Detection of task-associated brain states could ultimately be a closed-loop strategy for delivering real-time therapy to patients with mental illness.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

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**Topic:** G.03. Emotion

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**Title:** Interhemispheric paired associative stimulation of the prefrontal cortex jointly modulates frontal asymmetry and emotional reactivity

**Authors: *S. ZIBMAN**, E. DANIEL, U. ALYAGON, A. ZANGEN
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**Abstract:** Asymmetry of frontal alpha power has a long history of association with emotional regulation and processing. Typically measured by EEG, the relative activation of the right and left lateral prefrontal cortex (LPFC) is correlated to various emotional responses and an imbalance is associated with psychological conditions such as depression and aggression.
A major challenge in determining the role of frontal asymmetry in emotion is that while the

correlation between deficits in lateralization and in cognitive functions has been established, a causal relationship has not been fully demonstrated. One technique that can be used to alter connectivity and establish causality in the brain is paired associative stimulation (PAS) which, through the coordinated stimulation of two regions by two TMS coils, targets the intervening connectivity. The PAS protocol is based on Hebbian plasticity.
Here we investigate the effects of interhemispheric PAS between the left and right LPFC on attentional bias to emotional stimuli. 27 healthy subjects were recruited for a three session, sham-controlled crossover study, receiving left to right PAS (LR-PAS), right to left PAS (RL-PAS) and sham during different weeks. The protocol consisted of 210 pulse pairs with a lag of 8ms. Subjects performed an emotional reactivity task, in which participants are asked to respond to the color of visual stimuli, in this case faces, with different emotional content, assessed by measuring attentional bias, and brain activity was recording with EEG both at rest and in response to single pulse stimulation prior to and following the stimulation period.
Our results reveal that LR PAS increases attentional bias while increasing right frontal asymmetry whereas RL PAS decreased the attentional bias while decreasing right frontal asymmetry ($F(2,24) = 3.266$, $P=0.05$ and $F(2,27) = 5.936$, $P=0.005$ for attentional bias and frontal asymmetry respectively). These results confirm a relationship between frontal alpha asymmetry and attentional bias.
PAS induces an increase in interhemispheric signal propagation (ISP) only in the direction of the PAS protocol (left to right for LR-PAS and right to left for RL-PAS) and not in the reverse direction (3-way ANOVA $F(2,27) = 3.15$, $p = 0.05$ ). This indicates that PAS effects connectivity specifically in the direction of the stimulation.
This is the first demonstration of PAS's effectiveness in inducing cognitive changes by targeting interhemispheric PFC connectivity in a directional manner. Furthermore, by combining TMS with EEG, we provide a toolbox for evaluating effectiveness of PAS protocols that may facilitate development of novel therapies.

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**Poster**

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**Topic:** G.03. Emotion

**Support:** NIH Grant R00 HD065839

**Title:** Childhood exposure to violence predicts altered neural circuitry for emotion regulation in adulthood

**Authors: *S. S. MATTHEISS**, H. J. LEVINSON, N. ABOUKAFF, W. W. GRAVES
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**Abstract:** It is often suggested that early experiences of adversity, such as exposure to violence, alter how people process reward and threat. Previous studies of the neural basis of acute and chronic stress have shown alterations in connectivity between frontal and subcortical regions, corresponding to differential reward and threat processing. However, no studies to our knowledge have examined the particular effects of high exposure to community violence during childhood on resting state functional connectivity, a measure of the organization and communication among neural regions. The current study aims to elucidate such effects by conducting a between-group resting state functional connectivity analysis comparing individuals reporting high compared to low exposure to violence during the ages of 3 to 14 years. Participants were undergraduate and graduate students from the Rutgers University community, ages 19 to 32 years. Each group consisted of 14 participants, with socioeconomic status, reported levels of current exposure to violence, gender, verbal intelligence, and age matched between groups. Functional magnetic resonance imaging resting state data were collected while participants viewed a fixation cross in the scanner for seven minutes. The ventromedial prefrontal cortex (vmPFC) was entered as a seed region, given previous research demonstrating that this region regulates subcortical regions involved in threat and reward response. We predicted decreased connectivity between vmPFC and subcortical regions, such as the amygdala, for individuals exposed to high compared to low levels of violence during childhood. Results supported our predictions, with individuals reporting high compared to low levels of exposure to violence during childhood demonstrating negative connectivity with vmPFC and the left amygdala, implicated in threat processing, as well as the bilateral parahippocampal gyrus, implicated in both memory and processing negative affective information. These results suggest that exposure to violence during the ages of 3 to 14 may alter functional connectivity between vmPFC and the amygdala, a neural circuit involved in the regulation of emotional responses. These findings are consistent with previous studies demonstrating alterations in prefrontal-subcortical circuits due to exposure to stress, but extend such findings to include childhood exposure to violence. This study offers evidence supporting the claim that students in urban academic settings, where neighborhood crime rates are high, may benefit from interventions designed specifically to capitalize on such altered neural circuitry.

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**Poster**

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**Topic:** G.03. Emotion

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**Title:** Affective style modulates the relationship between cumulative violence exposure and change in functional connectivity after stress-induction

**Authors: *H. E. DARK**[1], N. G. HARNETT[1], A. M. GOODMAN[1], M. D. WHEELOCK[2], S. MRUG[1], M. A. SCHUSTER[3], M. N. ELLIOTT[4], S. TORTOLERO[5], D. C. KNIGHT[1]
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**Abstract:** Chronic stress can lead to changes in brain connectivity patterns and associated changes in psychological functioning. Greater levels of violence exposure, a type of chronic stressor, is associated with increases in emotion dysregulation and stress reactivity. Affective style reflects one's interpretation of stressful events and can also affect stress reactivity. Resting state functional connectivity (rsFC) is an index of brain connectivity patterns used to identify changes in brain function. Changes in rsFC are associated with deficits in emotion regulation and have been used to assess stress-induced variations in brain connectivity. The present study sought to examine the effects of violence exposure and affect on stress-induced changes in rsFC. Participants completed two 6-minute resting state functional magnetic resonance imaging (fMRI) scans, one prior to (pre-stress), and one after (post-stress) completing an adaptation of the Montreal Imaging Stress Task. FMRI data were obtained using a 3T Siemens Allegra scanner. The amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC) were used as seed regions for connectivity analyses. A linear mixed effects model analysis was conducted for each region to determine whether amygdala, hippocampus, and vmPFC-whole brain functional connectivity differed pre- to post-stress by cumulative violence exposure (CVE) and affect. All significant clusters were corrected for multiple comparisons ($p_{FWE}$=.05). There was a significant interaction between affect and CVE in predicting changes in amygdala, hippocampus, and vmPFC rsFC pre- to post-stress ($p_{FWE}$=.05). Positive, but not negative affect modulated the relationship between CVE and changes in hippocampus-dorsolateral prefrontal cortex (dlPFC) and amygdala-dorsomedial prefrontal cortex (dmPFC) rsFC. Specifically, those with low positive affect and high CVE exhibited greater changes in rsFC. Negative, but not positive affect modulated the relationship between CVE and changes in vmPFC-dlPFC rsFC such that those with moderate CVE and high, but not low negative affect, exhibited greater changes in rsFC pre- to post-stress. In the present study, the modulatory effects of affect on the relationship between rsFC and CVE suggest that low positive emotions and high negative emotions coupled with higher CVE contribute to greater changes in stress-induced brain connectivity. Findings provide insight into the complexities through which affect and violence exposure affect brain functioning and coincide with the literature that demonstrates that fronto-limbic brain regions mediate the emotional response to stress.

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**Poster**

**514. Circuits Underlying Emotional States**

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**Topic:** G.03. Emotion

**Support:** Marie Skłodowska-Curie Post-doctoral Fellowship (Call: H2020-MSCA-IF-2014) by the European Commission

**Title:** Time-modulated neural networks support a positivity bias in later life

**Authors: *E. SOLESIO-JOFRE**, M. HERNÁNDEZ-LORCA, L. CARRETIÉ
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**Abstract:** This Project is funded by a Marie Skłodowska-Curie Post-doctoral Fellowship (Call: H2020-MSCA-IF-2014)
Aging is a primary health concern for the entire world. Pessimistic perspectives characterizing aging as a time of profound physical, cognitive and emotional losses have been relieved by recent research illustrating improved well-being and emotional self-regulation in later life. Specifically, an age-related increase in the preference for positive over negative information in attention and memory, namely the positivity effect, seems to relate to a better cognitive functioning. However, several studies have challenged the reliability of this effect. The objectives of the present study were two-folded. First, to examine one crucial moderator that may affect the consistency of the positivity effect, which is related to the “experimental constraints” imposed by certain tasks. Second, to examine the neural underpinnings of the positivity effect with electroencephalography (EEG). To this end, 30 young and 30 older individuals performed a memory task with emotional material that manipulated low and high cognitive demands while participants were recorded with EEG. Behavioural data was analysed under the frame of the Signal Detection Theory. We employed source reconstruction analysis for EEG data in order to localize age differences in neural activity (work in progress). Our results indicated that older adults exhibit a reduced ability to distinguish old trials from new trials, and they are more prone to respond “old” when the trial is “new”, for positive stimuli compared to young adults in the less demanding condition. This effect is supressed in the higher demanding condition. These findings suggest that positive stimuli may generate higher interference than negative or neutral stimuli in emotional recognition with age. Additionally, cognitive demands seem to modulate such a positivity bias in older individuals. Regarding our EEG results, we expect such a positivity bias to be associated with a time-modulated prefrontal network.

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**Title:** Cardiac and respiratory physiological noise corrections improved resting state functional connectivity in the limbic areas

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**Abstract:** Blood oxygenation level-dependent (BOLD) signal measured using functional MRI (fMRI) observe spontaneous fluctuations during resting state (rs) even in the absence of an externally prompted task. These fluctuations contain physiological noise consists of cardiac pulsation and respiration, and these noises may influence the functional connectivity. Purpose of this study is to clarify the influence of physiological noise on the rs-fMRI signal, especially on limbic areas. Emotion such as anxiety state affects on respiratory activities, and olfaction which relatively associated with respiratory changes, these emotion-related respiratory changes involve activation of the limbic areas, especially the amygdala. Our hypothesis is that functional connectivity between the amygdala and other limbic areas may be influenced by respiratory-related fluctuation rather than connectivity between other cortical areas. Twelve healthy adults were participated in this study, and an informed consent approved by Showa University Ethical Committee was obtained from each subject. rs-fMRI was measured with a clinical 3T scanner (MAGNETOM Trio A Tim System, Siemens) with a 32-channel head coil. Functional imaging was acquired with multiband (MB = 4) accelerated gradient echo echo-planar imaging exciting four slices with increasing temporal resolution. Cardiac pulse wave and respiration were simultaneously recorded with whole-brain rs-fMRI to retrospectively correct physiological noise using DRIFTER TOOLBOX (SPM8). Functional connectivity between 116 nodes defined by Automated Anatomical Labeling (AAL) during resting sate fMRI time-series was tested with or without physiological noise correction. Pearson's correlations coefficients between nodes where calculated by using DPARSF software, and comparison were performed with analysis of variance and post-hoc using Bonferroni test for three groups' comparisons; session without both

cardiac and respiratory noise correction, session with only cardiac noise correction and session with both cardiac and respiratory noise correction. Our results suggest that the both cardiac and respiratory noise correction increased signal-to-noise-ration, and showing improved functional connectivity, especially, the connectivity between limbic areas para-hippocampus and amygdala, and basal ganglion.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** G.03. Emotion

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**Title:** Cortical circuit dynamics during punishment-resistant alcohol drinking

**Authors: *C. SICILIANO**, Y. LEOW, X. CHEN, E. Y. KIMCHI, C. M. VANDER WEELE, K. M. TYE
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**Abstract:** A great deal of research has highlighted the role of the medial prefrontal cortex (mPFC) in encoding motivational value and decision making. Further, alcohol-induced plasticity in mPFC has been implicated in aberrant alcohol drinking behaviors; however, we have little understanding of how neurons in mPFC are encoding alcohol related stimuli in real-time, and what downstream circuits are involved. Recently, we identified two projector populations in mPFC, to nucleus accumbens (NAc) or dorsal periaqueductal gray area (dPAG), which divergently route information related to positive and negative unconditioned stimuli, respectively. Here, we sought to dissect the role of these projection-defined subpopulations

within mPFC in associative learning and punishment-resistant alcohol drinking. Using a dual virus approach we selectively expressed the genetically encoded calcium indicator GCaMP6m in mPFC projecting to NAc or dPAG. By implanting a GRIN lens into the mPFC and attaching a miniature head-mounted microscope we were then able to record calcium dynamics with single-cell resolution during a novel Pavlovian conditioning task for alcohol, or alcohol adulterated with the bitter tastant, quinine. Using this alcohol seeking task, where the strength of alcohol conditioned cues and punishment-resistant alcohol consumption were tested before and after binge exposure to alcohol, we found that binge exposure produced wide individual variations in the development of punishment-resistant alcohol drinking. Further, the activity of the pathways tracked stimulus value, and differed between punishment-resistant and punishment-sensitive drinkers where resistance was associated with decreased activity of mPFC:dPAG to aversive stimuli. Together, our results support a model where activation of the mPFC:dPAG circuit encodes aversive stimuli and produces avoidance. Further, dysregulation of this pathway resulting from chronic alcohol use may blunt responsiveness to aversive stimuli and result in inflexible, punishment-resistant alcohol drinking.

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**Poster**

**514. Circuits Underlying Emotional States**

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**Topic:** G.03. Emotion

**Support:** Werner Reichardt Center for Integrative Neuroscience (H.C.E.)

Max Planck Institute for Biological Cybernetics (N.K.L.)

International Max Planck Research School (F.H)

**Title:** Insular projections to the parabrachial nucleus in the macaque monkey

**Authors: *F. HORN**[1,2,3], T. O. SALEH[1,2], N. K. LOGOTHETIS[2,4], H. C. EVRARD[1,2]
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**Abstract:** The large spindle-shaped von Economo neuron (VEN) occurs in a specific architectonic area (‘VEN-area’) in the macaque anterior insula (Evrard *et al.*, Neuron, 2012, 74:482-9). Given its relatively large size and localization in layer 5a, the VEN likely projects to

distant brain regions. We recently reported that one of this target is the midbrain periaqueductal gray (PAG). Here we examined the insular projections to another key homeostatic center, the parabrachial nucleus (PBN) using injections of anterograde tracers in AIC and of retrograde tracers in PBN. Injections of biotin-dextran-amine (BDA) in the insular area containing VENs produced sparse but consistent anterograde labeling in both the medial and lateral aspects of the PBN. Injections of retrograde cholera toxin b (CTb) or fluorescent dextran in PBN invariably labeled cortical projections neurons on both side of the neocortex. However, unlike for our prior injections in PAG, the AIC, including the VEN area, was almost the only cortical region labeled. The retrogradely labeled neurons included pyramidal neurons as well as VENs and their companion Fork neurons (FNs). These results are consistent with our microstimulation works showing activation of both left and right PBN with microstimulation of either the left or right AIC (see Smuda et al, this meeting). They are also consistent with our recent collaborative evidence that the human VEN area is strongly functionally connected with PBN and that this functional connection is massively altered in coma patients with a brainstem lesion (Fischer et al., Neurology, 2016, 90:143-51). Finally, they suggest that the relatively large VEN and FN might provide rapid cortical efferent projections for the regulation of brainstem autonomic processing both at the afferent (PBN) and efferent (PAG) stages.

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**Poster**

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**Topic:** G.03. Emotion

**Support:** Werner Reichardt Center for Integrative Neuroscience

Max Planck Institute for Biological Cybernetics

International Max Planck Research School

**Title:** Microstimulation of the anterior insular cortex in the macaque monkey

**Authors: *J. SMUDA**[1,2,3], C. KLEIN[1], Y. MURAYAMA[1], T. STEUDEL[1], E. KRAMPE[1], A. OELTERMANN[1], J. WERNER[1], N. LOGOTHETIS[1,4], H. C. EVRARD[1,2]
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**Abstract:** The anterior insular cortex (AIC) is often regarded as a key “node” of the saliency network with a role in coordinating brain network activity after detection of homeostatic

changes. In addition, distinct areas of the AIC project to homeostatic brainstem centers and could therefore act as a cortical output stage for the concurrent regulation of physiological and behavioral emotional responses to salient events. Given the possible role of the AIC in switching brain network dynamics and in descending autonomic regulations, we combined electrical microstimulation and functional magnetic resonance imaging (fMRI) using a 7T scanner to examine the effect of electrical microstimulation of the AIC on the blood-oxygen-level-dependent (BOLD) signal in both the subcortical homeostatic centers and the neocortex in 5 anesthetized macaque monkeys. Single channel glass isolated iridium electrodes were used to deliver 200-μs biphasic charge-balanced pulses with stimulation frequencies of 5, 40, 60 and 100 Hz during two-shot echo-planar imaging (EPI) with a temporal resolution of 2 seconds (Logothetis et al. Nature Nsci 2010 13:1283-91). Electrical microstimulation of the left or the right AIC produced strong positive and negative BOLD signal changes in both cortical and subcortical regions. In some sessions, there was a distinct but varying activation of all subcortical centers known to receive monosynaptic projections from the AIC (hypothalamus, periaqueductal gray, parabrachial nucleus). However, in most sessions, this pattern was accompanied or replaced with massive activation or deactivation of the neocortex, in particular primary sensory areas, with a trend for the left and right AIC to produce more prevalently cortical activations and deactivations, respectively. These effects, coupled with our tract-tracing and NET-fMRI data, begin to unravel the functional organization underlying the role of the AIC in brain network dynamics and brainstem autonomic control regulation.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

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**Program#/Poster#:** 514.24/SS13

**Topic:** G.03. Emotion

**Support:** Werner Reichardt Center for Integrative Neuroscience (H.C.E.)

Max Planck Institute for Biological Cybernetics (N.K.L.)

International Max Planck Research School (J.S.)

**Title:** NET-fMRI examination of the relation between the anterior insula and whole-brain activity in the macaque monkey

**Authors: *C. KLEIN**[1], J. SMUDA[1,2,3], Y. MURAYAMA[1], T. STEUDEL[1], E. KRAMPE[1], A. OELTERMANN[1], J. WERNER[1], N. K. LOGOTHETIS[1,4], H. C. EVRARD[1,2]
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**Abstract:** The central representation and the goal-directed control of bodily states are integrated in the anterior insular cortex (AIC) as core processes underlying the 'subjective' component of emotion and cognition. The AIC is often regarded as a key "node" of the saliency network with a role in coordinating brain network activity upon the detection of homeostatic changes. A model proposed that the preferential representation of parasympathetic and sympathetic activity in the left and right AIC underlies appetitive and aversive emotions, respectively (Craig TICS 2005 9:566-71). Given the possible role of the AIC in switching brain network dynamics, we examined whether this asymmetry occurs in functional relation of the AIC with the rest of the brain. To this end we used multi contact laminar electrodes to record neural activity from the left and right AIC in parallel while simultaneously acquiring functional magnetic resonance imaging (fMRI) scans in four rhesus macaque monkeys. The electrodes were placed in the AIC area containing the von Economo neurons (or 'VEN area'), an area shown previously to be larger and independently contain more VENs on the right than on the left side (Evrard et al. Neuron 2012 74:482-9). The ongoing spontaneous neuronal activity was analyzed focusing on the local field potential (LFP) gamma band (56-79 Hz) where frequent increases in amplitude could be observed. These gamma events were in most cases unilateral, with occurrence either in the left or in the right VEN area in the majority of the cases and only few cases where gamma band activity increased simultaneously on both sides. Following the detection of these gamma events, their occurrence was used to trigger and average the blood-oxygen-level dependent (BOLD) signal from the fMRI scans, a method called 'neural-event-triggered fMRI' (NET-fMRI) (Logothetis et al. Nature 2012 491:547-53). The examination and mapping of the BOLD signal change during asymmetric events revealed markedly different patterns of activation and deactivation in vast regions of the brain. These effects might substantiate a fundamental autonomic forebrain asymmetry balancing brain dynamics to produce nurturing and expending behaviors and feelings in a homeostatically optimal manner.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 514.25/SS14

**Topic:** G.03. Emotion

**Support:** Werner Reichardt Center for Integrative Neuroscience

Max Planck Institute for Biological Cybernetics

International Max Planck Research School

**Title:** Functional mapping of insular cortex activity using gustatory and interoceptive stimuli

**Authors: *R. E. HARTIG**[1,2,3], A. VEDOVELI[1,2,3], F. HORN[1,2,3], C. BATTAL[4,5], G. CHÁVEZ[1,2,3], E. KRAMPE[2], T. STEUDEL[2], J. WERNER[2], A. OELTERMANN[2], N. K. LOGOTHETIS[2,6], H. C. EVRARD[1,2]
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**Abstract:** The cortical representation and processing of sensory afferent impulses is crucial for the fine coordination of complex brain and bodily responses to salient events. One specialized brain region, the insular cortex (IC), represents sensory inputs related to interoception and gustation. We examined the functional organization of distinct IC subregions using multi-modal stimuli with fMRI and electrophysiology in macaque monkeys and, to a lesser extent, fMRI in humans. The gustatory pathway was stimulated using various sets of taste stimuli, including sweet, sour and salty tastants applied to the tongue at high- and low-intensity concentrations. Despite individual variations in both species, consistent BOLD signal changes emerged in the anteroposterior mid-dorsal fundus and the most anterior aspect of the fundus, with a distinct separation of several millimeters from the middle representation. We also probed the interoceptive pathway using transcutaneous stimulation of the auricular branch of the vagus nerve (tVNS), rectal distention (RD), and local skin temperature changes in macaque monkeys. Thermal stimulation of the hand and foot consistently produced positive BOLD signal changes in a region posterior to the middle taste representation. Both RD and tVNS variably activated a smaller region near the taste representation and another region in the ventral anterior aspect of the IC, a region which has been related to a network of high-order cognitive functions and top-down influence on the autonomic nervous system. Electrophysiological recordings throughout the insula in macaque monkeys largely confirmed this topography. These non- or minimally-invasive stimulations of the primary interoceptive cortex provide the first multi-modal mapping of bodily functions in the IC. This work is an important first step towards understanding the neurobiology of subjective feelings and the relation of brain and bodily states during high-order emotional and cognitive functions.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** G.03. Emotion

**Support:** Fordham University Undergraduate Research Grant

**Title:** Characterization of the intrinsic functional connectivity of the habenula in children with adhd

**Authors: *M. ARFUSO**[1,1], A. K. ROY[1], F. X. CASTELLANOS[2], R. SALAS[3]
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**Abstract:** The habenula is a small brain region that is a part of the epithalamus. It directly regulates dopaminergic and serotonergic circuits through the ventral tegmental area and substantia nigra. Both of these circuits are implicated in reward processing, and show deficits in children with ADHD, suggesting that habenula function may be irregular in ADHD. Because the habenula is thought to contribute to reward prediction error, habenular function may also be associated with the lower frustration tolerance often observed in children with ADHD and other disruptive behavior disorders. To test these hypotheses, this study examined the intrinsic functional connectivity (iFC) of this brain region in children (ages 5- 9 years) with (n=41) and without ADHD (n= 45), and in children with low frustration tolerance as evidenced by severe temper outbursts (TO; n=61). Following psychological assessments, children participated in a 6-minute resting state scan. Neuroimaging preprocessing was done using the Configurable Pipeline for the Analysis of Connectomes (C-PAC). Seed-based iFC used 1mm radius habenula regions of interest, identified individually from normalized T1 weighted images. Groups did not differ in age, sex, or movement during the scan. Results showed negative functional connectivity between the left habenula and the putamen in the ADHD group, as compared to positive connectivity in the control group. Additionally, three iFC clusters showing significantly decreased left habenula iFC in the ADHD group as compared to the TO group: the posterior cingulate, precuneus, and superior temporal gyrus. The right habenula analysis yielded two clusters: the posterior cingulate and the precuneus showing negative iFC in the ADHD group and positive iFC in the TO group. Overall, our results suggest that disruption in the iFC in the habenular network of children with ADHD through possible dysregulation of dopaminergic pathways. Further, alternative functional connections of the right and left habenulae with cortical regions appear to play a role in frustration tolerance and possibly emotion regulation.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

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**Program#/Poster#:** 514.27/SS16

**Topic:** G.03. Emotion

**Title:** Frontal, amygdalar, and temporal convergence in the ventral striatum: Implications for Huntington's disease

**Authors:** *E. H. YATES[1], ***E. H. YATES**[1], J. A. BURK[2], S. N. HABER[3]
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**Abstract:** Huntington’s disease (HD) is a debilitating neurodegenerative disease that is part of a class of diseases affecting the basal ganglia. Impaired negative emotion recognition is a common and early symptom of HD, and entails the patient being unable to properly identify negative emotions on human faces. Through analysis of cell label patterns in a macaque cortex with a retrograde tracer, a region in the ventral striatum has been identified with the potential to function as a critical hub in the emotion processing networks. This region of the striatum receives projections from cortical and subcortical regions involved with emotion processing, including the amygdala, ventromedial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, and temporal lobe. Analysis of the region of the striatum receiving the projections above will be evaluated to provide more insight into the link between the progression of the pathophysiology of HD and the symptoms of HD over time. The identification of this hub has the potential to broaden our understanding of symptomatology and progression in HD, contribute to other projects in neuropsychiatric disorders involving the striatum, and provide further data for the study of brain connectivity as a whole.

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**Poster**

**514. Circuits Underlying Emotional States**

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**Topic:** G.03. Emotion

**Support:** NINDS R01NS024760

**Title:** Cortical connections of primate subgenual cingulate area 25

**Authors: *M. P. JOYCE**[1], H. BARBAS[2]
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**Abstract:** Area 25 (A25) has been implicated in emotion and mood disorders. This cortical area is found deep in the ventral and posterior aspect of the subgenual cingulate region. To date, only a few studies have reported on some cortical connections of A25, providing valuable information but an incomplete picture. Using neural tracers in rhesus monkeys, we examined the full complement of A25 connections at laminar and cellular resolution. Connections within the prefrontal cortex (PFC) composed the densest pathways to A25, specifically the medial and posterior orbital PFC and the frontal pole (area 10). We found moderately dense A25 afferents from the temporal pole, the medial temporal cortices, and temporal auditory association cortices. A25 targets and receives connections mostly from superficial layers of eulaminate areas that have more developed laminar structure, such as the temporal auditory association areas. Conversely, A25 tends to target and receive connections from middle to deep layers of agranular areas that have more rudimentary lamination, such as the medial temporal cortices and anterior insula. Patterns of A25 connections are consistent with the rules of the Structural Model, which predict laminar specific connections based on differences in laminar structure between linked cortices. A25 is a dysgranular limbic cortex, with strikingly dense deep layers relative to superficial layers. Connections with more elaborately layered cortices support a strong feedback-type role of A25 in corticocortical communication. Because cortical layers uniquely contribute to the columnar microcircuitry and are differentially populated by functionally distinct classes of inhibitory neurons, laminar-specific interactions have major implications for the functional impact of the different corticocortical pathways of A25. Laminar-specific interactions are also relevant for how A25 is differentially recruited in functional networks, such as affective networks or the Default Mode Network (DMN), both of which exhibit functional connectivity with A25. Within the context of the DMN, laminar specific interactions may be relevant for the switch between task-dependent and default modes of processing.

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**Poster**

**514. Circuits Underlying Emotional States**

**Location:** Halls A-C

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**Topic:** G.03. Emotion

**Support:** NIMH Grant R01MH057414

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**Title:** Simulating thalamo-cortical dynamics underlying discontinuous tracking in schizophrenia

**Authors: *Y. J. JOHN**[1], B. ZIKOPOULOS[1], D. H. BULLOCK[2], H. BARBAS[1]
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**Abstract:** Schizophrenia is a severe psychiatric disorder marked by disruptions to emotional balance, cognition, and perception. As with many psychiatric disorders, no single cause has been associated with the observed symptoms. These symptoms are qualitatively disparate, and therefore do not readily suggest any common neural mechanisms. Genetic, experiential, and environmental factors have been found to correlate with schizophrenic symptoms, but a consensus on how such factors trigger symptoms has proven elusive. However, abnormalities in the cortico-reticulo-thalamic circuit are observed in patients with schizophrenia and in animal models of the disorder. Here we integrate these findings by simulating a formal circuit model of interactions among cortex, thalamus, and the thalamic reticular nucleus (TRN). To demonstrate how the model behaves in both normal and abnormal modes, we simulated behavioral tasks that require smoothly tracking a moving stimulus across a stationary background of distracters. Eye movements patterns in such tasks distinguish schizophrenic patients from healthy controls. In schizophrenic patients, ocular tracking attempts exhibit many discontinuities, which entail frequent catch-up saccades. In the model, TRN neurons enable lateral inhibition of thalamo-cortical neurons, which - if strong enough - mediates maintained target selection and suppression of distracters. Local inhibitory interneurons in cortex regulate the strength and spread of cortico-reticular and cortico-thalamic excitation, and thereby the net strength of lateral inhibition. Our simulations show that weakened inhibition, from cortical interneurons or TRN neurons or both, can lead to discontinuities of smooth tracking that necessitate frequent catch-up saccades. Abnormal oscillatory modes in the thalamus and TRN, such as sleep-related rhythms intruding into the waking state, can also disrupt lateral inhibition and thereby lead to abnormal tracking. If the disordered circuit mechanisms that render tracking discontinuous also act at higher levels of the cognitive hierarchy, they may help explain schizophrenics' disrupted ability to maintain attention on a single organizing representation or theme across the distracting thoughts that often emerge during language production and other rule-guided performances. Thus, the model specifies possible causal mechanisms by which abnormalities in the cortico-reticulo-thalamic circuit may contribute to common behavioral symptoms of schizophrenia.

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**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 515.01/SS19

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Does nature benefit everyone? Salivary cortisol responses of wilderness therapy clients

**Authors: A. K. EAGLE**[1], *C. L. FRANSSEN[2]
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**Abstract:** Wilderness therapy, a subset of the broader field of outdoor therapy, is used to treat clients with a range of issues from addiction to emotional struggles (Russell, 2001). Wilderness therapy has been shown to effectively reduce mental health symptomology, and investigations are underway in several labs to best understand the type of client most positively affected by this intervention (e.g., Bettmann et al., 2013; Hoag et al., 2014; Russell et al., 2015). Mental health outcomes are routinely evaluated through self-report, family report, and clinician report on standardized measures such as the Y-OQ. In this study, we sought to evaluate changes occurring during a wilderness therapy experience through neuroendocrine measures. In this project, we partnered with Blackwater Outdoor Experiences®, a wilderness therapy group based in Midlothian, VA. We collected saliva samples and survey data before, during, and after a 22-day wilderness therapy trip. Previous studies, such as those listed above, indicate high response rates among patients with primary diagnoses of substance abuse, mood disorders, and behavioral disorders, often with comorbid anxiety or anxiety disorders. Therefore we focus our initial study on stress-related hormones, namely cortisol. Informed by the clinical profiles of wilderness therapy clients, we examined the effects of gender, age, and primary diagnosis on cortisol variation over the treatment program in an effort to further understand the type of client that will benefit most from wilderness therapy. Our findings represent the first integrative analysis of wilderness therapy clients that includes neuroendocrine data.

**Disclosures: A.K. Eagle:** None. **C.L. Franssen:** None.

**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

**Location:** Halls A-C

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**Program#/Poster#:** 515.02/SS20

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH 1R01GM111421

**Title:** Dezocine for opioid addiction and its molecular targets

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**Abstract: Synopsis:** Opioid dependence continues to be a major public health issue without optimal therapeutics. The present study investigated the therapeutic potential of dezocine, a non-addictive opioid, to attenuate naloxone-precipitated morphine withdrawal syndrome in a rat addiction model. The intensity of the morphine withdrawal syndrome was reduced doze-dependently in rats treated with dezocine comparable to that with buprenorphine. Chronic morphine administration through repeated subcutaneous injections induced astrocytes activation in nucleus accumbens, which was attenuated by dezocine and buprenorphine. Dezocine blocked the agonist-induced kappa opioid receptor internalization, using a fluorescently tagged kappa opioid receptor over-expressed neuroblastoma cells *in vitro.* However, buprenorphine blocked the receptor internalization with higher potency than dezocine. Interrogation of 317 human G protein coupled receptors via a G protein-independent β-arrestin-recruitment and radioligand binding assays for 44 G protein coupled receptors, ion channels and transporter proteins indicated that morphine, dezocine and buprenorphine have different sets of molecular targets. It was revealed that Neurokinin 1 Receptor is potentially novel unique molecular target for dezocine for its anti-addictive properties. Furthermore, while dezocine inhibits norepinephrine and serotonin reuptake as we demonstrated previously, buprenorphine did not interact with norepinephrine and serotonin transporters. Findings in this study suggest that dezocine could be an alternative medication for opioid addiction management and has different molecular targets from that of buprenorphine.
Significance Statement: This study provides evidence that dezocine, a partial mu opioid receptor agonist and kappa opioid receptor antagonist, could potentially be used for addiction management by using a rat morphine dependence model. It is important to note that dezocine is a non-addictive opioid that has been used in clinical practice for centuries. The molecular targets of dezocine are also investigated in parallel of morphine and buprenorphine, providing useful information for science communication in understanding molecular mechanisms for addiction and anti-addiction. Novel molecular targets are revealed for all three molecules. Dezocine is a neurokin 1 receptor agonist, which could potentially relate to its non-addictive property.

**References**

1. *J Opioid Manag.* 2016, **12**: 109-18.
2. *J Psychopharmacol* 2006, **20**: 806-814.
3. *Anesthesiology*. 2014,120:714-23.

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**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** MOST 2015CB553503

NSFC 91432303

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**Title:** Methadone induced retrieval extinction procedure inhibits the drug craving and relapse in heroin addicts under methadone maintenance treatment

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**Abstract: Background**: Conditioning between drug-associated environment cues (conditioned stimulus, CS) and drug effects (unconditioned stimulus, UCS) plays a major role in drug addiction, and responses to drug-associated cues persist during prolonged abstinence. We previously reported that CS memory retrieval-extinction procedure decreases relapse of cocaine and heroin seeking in rats and heroin craving in humans. However, the CS retrieval-extinction procedure could only erase drug memory associated with the reactivated CS, and it was not effective after prolonged abstinence. In contrast, the inhibitory effect of UCS retrieval-extinction manipulation on drug seeking in rats was also observed in the presence of cues that were not reactivated or after long-term abstinence. Using methadone as the UCS, the present study investigated the effect of UCS retrieval-extinction on cue induced drug craving and relapse in heroin addicts. **Methods:** Eighty-nine male heroin addicts under methadone maintenance treatment were randomly divided into 3 groups: 1) Methadone, 2) Methadone+10-min delay+ extinction, 3) Methadone+6-h delay+ extinction. The subjects in Group 1 took methadone as usual, while the subjects in Group 2 and 3 underwent extinction sessions 10 min or 6 h after methadone intake 3 times per week for 4 weeks. All the subjects were followed up for 6 m to test the changes of heroin craving, relapse, and dose of daily methadone use. We also conducted morphine urine tests each week during the 4 weeks' intervention and each month during the follow up. **Results:**Seventy-eight heroin addicts completed the intervention and were included for statistical analysis. There was no significant difference in cue induced heroin craving, dose of daily methadone intake, depression, anxiety, as well as demographic characteristics at baseline among the three groups. After 4 weeks' methadone-induced retrieval extinction manipulation, both the subjects in Group 2 and Group 3 showed significantly decreased heroin craving compared with Group 1. The inhibitory effect on heroin craving persisted for 4 m in Group 2, but only persisted for 2 m in Group 3. Both the accumulative drop-out rates and relapse rates of Group 2 were significantly lower than Group 1 and Group 3. **Conclusions**:These findings demonstrated that the methadone induced retrieval extinction strategy could be a promising method for decreasing drug craving and relapse in heroin addicts.

**Disclosures:** **P. Wu:** None. **J. Yue:** None. **X. Guo:** None. **X. Lin:** None. **S. Chen:** None. **L. Lu:** None.

**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 515.04/SS22

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Employee on duty

**Title:** Beta-caryophyllene: A promising dietary CB2 receptor agonist for treatment of addiction in experimental animals

**Authors: X.-F. WANG**[1], G.-H. BI[2], Y. HE[3], E. L. GARDNER[4], *Z. XI[3]
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**Abstract:** Two types of cannabis oils are used by humans - hash oil and hemp oil. *Hash oil* is an oleoresin extracted from the buds, flowers and leaves of female marijuana, while hemp oil is extracted from the seeds of the hemp plants. Since hash oil contains higher levels of delta9-THC, it has addictive potential and is used for medical or recreational purposes. In contrast, hemp oil contains a high level of cannabidiol but a low level of delta9-THC; it is used as a food oil (essential oil) or dietary supplement. Beta-caryophyllene (BCP) is a typical ingredient in essential oils. It has been used as a food additive due to its distinctive taste or as a cosmetic additive in various skin care products due to its pleasant nutty smell. In 2008, it was identified as a selective CB2R agonist (Gertsch et al., PNAS, 2008). We have recently reported that cannabinoid CB2Rs are expressed in midbrain dopamine neurons and functionally inhibit DA neuron activity and cocaine self-administration behavior. In the present study, we investigated the potential utility of BCP in treatment of drug addiction. We found that: 1) low doses of BCP (3-25 mg/kg, i.p.) dose-dependently inhibited nicotine or methamphetamine self-administration, while higher doses (50, 100 mg/kg) of BCP are required to inhibit self-administration of cocaine, heroin or food in rats or mice; 2) Pharmacological blockade or genetic deletion of CB2Rs (in CB2-KO mice) blocked low dose BCP-induced inhibition of nicotine or methamphetamine self-administration, but had no effect on high dose BCP-induced inhibition of drug self-administration, suggesting that both CB2R and non-CB2R mechanisms are involved; 3) high doses of BCP also significantly inhibited cocaine- or cue-induced reinstatement of drug-seeking behavior; 4) This reduction in drug-taking and drug-seeking is not due to sedation or locomotor impairment since BCP, at 3-50 mg/kg, had no effect on open-field locomotion or rotarod locomotor performance; 5) BCP itself failed to maintain self-administration in cocaine or heroin

self-administration rats, suggesting no addictive potential by itself; and lastly, 6) BCP, at 25-50 mg/kg, moderately decreased extracellular dopamine (DA) in the nucleus accumbens, while pretreatment with BCP failed to alter cocaine- or methamphetamine-enhanced extracellular DA, suggesting a non-DA mechanism involved. Together, the present findings suggest that BCP may be a promising dietary cannabinoid for treatment of drug abuse and addiction. (Supported by NIDA IRP)

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**Poster**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Medication Development Program funds, NIDA-IRP

NIA-IRP

**Title:** Characterization of the effects of typical and atypical dopamine uptake inhibitors and other centrally acting drugs on the ElectroEncephaloGram of freely moving rats

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**Abstract:** There is renewed interest in using electroencephalogram (EEG) as a tool to improve early diagnosis of neurological and behavioral disorders (i.e. ADHD, depression and schizophrenia) and also to assist the preclinical development of related pharmacotherapies. A preclinical assay becomes of value in drug development when effects of new chemical entities can be compared under the same conditions with those of known drugs to provide predictions on potential therapeutic effects. The aim of the current study is to establish an assay to rapidly determine EEG drug dose-effect curves in freely moving rats and evaluate its pharmacological selectivity by characterizing known compounds with different mechanisms of action and behavioral effects. EEG signals were collected from 6 stainless steel screws that served as electrodes implanted on the skull of male Sprague Dawley rats. These electrodes were connected through an electrode-interface board to a connector on the animal's head. During 60 to 150 min experimental sessions, EEG signals were recorded through a digital headstage in which signal was band passed between 0.1 to 250 Hz and digitized at 2 kHz. A pump was used to deliver, through an externalized jugular vein catheter, cumulative doses [mg/kg] of the typical dopamine

uptake inhibitor (DUI) cocaine [0.1-3.2] or methylphenidate [0.1-5.6], the atypical DUI modafinil [1-32], the mu-opioid agonist morphine [0.32-17.8] or the NMDA receptor antagonist ketamine [3.2-17.8]. EEG power spectrum was estimated using the short-time Fourier transform and grouped in 5 bands: Δ [0-4 Hz], θ [4-8Hz], α [8-13], β [13-30] Hz], γ [30-50 Hz]. Power spectral values were then normalized to the pre-infusion interval [baseline] and expressed as % of baseline. All the DUI dose-dependently decreased power of the β band to the same minimum [≈ 70%] while only the atypical DUI modafinil at a large dose increased power of θ waves. Both ketamine and morphine increased power [> 130%] of Δ, θ, α, β. Ketamine but not morphine also increased power of the γ waves. Therefore, typical and atypical DUI and drugs of other classes differentially affected EEG spectra showing distinctive features in the magnitude and direction of the effect on different frequency bands. Taken together these data suggest that the EEG can be used to rapidly screen new chemical entities for potential activity at specific pharmacological targets and to provide valuable information for guiding the early stages of drug development.

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**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

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**Program#/Poster#:** 515.06/SS24

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH grant DA035958

NIH grant AA02919

**Title:** Exercise-induced down-regulation of D2 autoreceptors in the nucleus accumbens

**Authors:** ***K. BILLS**[1], J. YORGASON[2], S. MCCARTHY[2], M. WOODBURY[2], S. STEFFENSEN[2]
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**Abstract:** The current consensus is that the rewarding and addictive properties of drugs of abuse, including alcohol, are mediated by dopamine (DA) neurotransmission in the mesolimbic system. Dopamine neurons express D2 autoreceptors (D2Rs) on cell bodies in the ventral tegmental area (VTA) and terminals in the nucleus accumbens (NAc). Dopamine activation of D2Rs at cell bodies inhibits DA neuron firing and DA activation of D2Rs at terminals decreases release of DA. D2R expression is directly proportional to DA levels and are reportedly in flux as the mesolimbic system progresses along a continuum of acute drug exposure to a state of drug dependence, presumably due to changes in extracellular DA concentrations. Mild to moderate

exercise has been shown to increase DA release in the NAc and high levels of exercise have been associated with various aspects of addiction including increased seeking behavior. Using *ex vivo* fast-scan cyclic voltammetry in the NAc, we evaluated the effects of three levels of exercise on D2R activity. Rats were exercised 5 days per week for 60 min/day day for 8-weeks. We tested paired-pulse responses to electrical stimulation to evaluate D2R activity. Typically, D2R activation results in decreased release during a secondary pulse at the tested intervals (10ms to 1s) causing inhibition of the paired-pulse ratio. We found that paired-pulse responses between 200ms and 1s were potentiated in medium and high intensity exercised rats compared to controls, suggesting a decrease in D2R activity in exercised rats. These data suggest that exercise does exhibit a dose-dependent effect on the mesolimbic DA system. Current studies are underway to examine D2R density changes and the effects of exercise intensity on acute ethanol exposure in naïve rats and withdrawal from chronic exposure in dependent rats.

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**515. Treatment Mechanisms for Substance Use Disorders**

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**Program#/Poster#:** 515.07/SS25

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Institutes for Behavior Resources Intramural Funds

**Title:** Behavioral economic demand metrics for abuse liability quantification and clinical treatment prediction

**Authors: *L. P. SCHWARTZ**[1], P. G. ROMA[2,3], J. E. HENNINGFIELD[4,3], S. R. HURSH[2,3], E. J. CONE[4], A. R. BUCHHALTER[4], R. V. FANT[4], S. H. SCHOLL[4]
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**Abstract:** Behavioral Economics provides a framework for quantifying drug abuse liability that can inform public health risk, clinical treatment, and research. Hypothetical purchase task questionnaires (HPTs), in which respondents report the number of units of a commodity they would purchase at various prices, provide a low-cost and sensitive method by which to measure and predict the appeal of pharmaceutical drugs that differ by formulation. However, the validity of this type of analysis must be empirically established by comparing essential value (EV) for different drugs across subgroups and time. This pilot study aimed to use hypothetical demand curves and the Exponential Model of Demand to assess the "essential value" (EV) of opioid

medications, specifically, easily tampered formulations vs. tamper-proof formulations. Participants were 25 methadone-maintained opioid dependent outpatients that used heroin as their primary drug prior to entering treatment. Of these, 32% reported experience manipulating prescription opioid pills. Participants filled out HPTs for standard pills, tamper-proof pills, alcohol, and cigarettes; questionnaires were framed within the time of the respondents' heaviest opiate abuse prior to enrolling in treatment. Some participants (n = 16) repeated the tasks after one year. At Time 1, participants had a higher EV for opiates than for the other drugs. Participants with manipulation experience (M) had a higher EV for standard pills than those with no experience (NM), but there was no difference in EV for tamper-proof pills between the two groups. The M group had a lower EV for the tamper-proof opiate pill than for the standard pill, while the NM group had no difference in EV for the two pill types. At Time 2, M participants had significantly higher EV for alcohol and both opiate pills than the NM group, but there was no longer a difference between the standard and tamper-proof pills. There were no differences in maximum demand or breakpoints between the two groups at Time 1 or 2. There was a positive correlation between the EVs of different drugs, and between some behavioral economic indices and treatment outcomes. Our results indicate that tamper-proof opiate pills have less value than standard pills for those who manipulate pills. The ability to accurately assess the abuse potential of opiate pill formulations requires a valid and reliable metric with which to measure the reinforcing value of a drug. HPTs provide sensitive measures of abuse potential that can distinguish between different formulations in relevant sub-populations, and may form the basis of quantitative individual drug demand profiles for predicting clinical treatment outcomes.

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**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Academy of Finland #256836

Finnish Alcohol Research Foundation

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**Title:** Serotonin transporter density in binge eating disorder and pathological gambling: A PET study with [$^{11}$C]MADAM

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**Abstract:** Behavioral addictions, such as pathological gambling (PG) and binge eating disorder (BED), appear to be associated with specific changes in brain dopamine and opioid function, but the role of other neurotransmitter systems is less clear. Given the crucial role of serotonin in a number of psychiatric disorders, we aimed to compare brain serotonergic function between PG, BED and controls.
Seven BED patients, 13 PG patients and 16 healthy controls were scanned with high-resolution positron emission tomography (PET) using the serotonin transporter (SERT) tracer [$^{11}$C]MADAM. The subjects were matched by sex and age. Both region-of-interest (ROI) and voxel-wise whole brain analyses were performed. ROIs were created using the anatomical parcellation with Freesurfer software. Non-displaceable binding potentials ($BP_{ND}$) were calculated using simplified reference tissue model with the cerebellar cortex as the reference region. Parametric images were normalized to the Montreal Neurological Institute standard space and analysed using general linear model with SPM8 software.
Patients with BED showed increased SERT binding in parieto-occipital cortical regions compared to both PG and controls (Figure 1) with parallel decreases of binding in the nucleus accumbens, inferior temporal gyrus and lateral orbitofrontal cortex. Greatest increases were observed in the superior parietal cortex where BED group had 122% higher $BP_{ND}$ compared to controls and 108% higher compared to PG patients ($p<0.001$). No differences between PG patients and controls were observed. There were no differences in BDI scores between PG and BED patients, and [$^{11}$C]MADAM $BP_{ND}$s did not correlate with BDI scores or body mass index. The results highlight differences in brain SERT function between BED and PG providing further evidence of different neurobiological underpinnings in behavioral addictions that are unrelated to co-existing mood disorder. The results provide a framework for additional studies that aim for development of syndrome-specific pharmaceutical treatments.

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**Poster**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** BSF Grant 2013323

**Title:** Infralimbic stimulation reduced cue-induced relapse to Cocaine seeking and normalize cue-induced electrophysiological activity in the rat conflict model

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**Abstract:** Relapse to drug use following a period of self-imposed abstinence is a major hallmark of drug addiction in general, and cocaine addiction in particular. In both humans and animal models, such relapse can be reliably triggered by exposure to drug-associated cues, a phenomenon termed cue-induced relapse (CIR). It has been suggested that CIR is, at least in part, the resultant of drug-induced changes of neuronal activity within the areas of medial prefrontal cortex (mPFC). To further explore this notion, we used a chronically-implanted bilateral linear microelectrode array (LMA) to Prelimbic (PL) and infralimbic (IL) areas of the mPFC in rats trained to self-administer (SA) cocaine or saline. The LMA were used to record local field potentials (LFPs) throughout the experiment, and to induce intracranial electrical stimulations (ICES) as a possible relapse prevention treatment. For the induction of self-imposed abstinence we used the conflict model, in which gradually increasing adverse consequences for drug seeking are represented by an electric barrier between the rat and the Cocaine-associated lever. Four groups of rats (n=9-13) were used: Saline SA + Sham ICES (Saline-Sham), Cocaine-Sham, Cocaine-PL, and Cocaine-IL. Following treatment, rats were subjected to CIR tests, where drug associated cues were presented every 2min, and the electric barrier was activated (conflict condition), while during a free-seeking test, cues were presented but the barrier was not activated. The results indicate that ICES of the IL, but not PL of cocaine-SA rats significantly reduced relapse rates and active-lever presses during CIR tests (compare to sham stimulation). On the other hand, active-lever presses of the Cocaine groups did not differ during the free-seeking test, and were significantly higher than that of the Saline group. In addition, an electrophysiology analysis demonstrates that repeated Cocaine SA is associated with increased cue-induced N1 and P1 amplitudes, and with increased alpha and beta power bands in the IL; but that IL-ICES normalized P1 amplitudes and beta activity. Taken together, it seems that repeated Cocaine SA is associated with increased saliency of the drug-associated cues, a tendency that can be normalized by stimulation of the IL mPFC. More specifically, it seems as IL-ICES can affect the motivation to obtain the drug but does not affect drug craving. Results of this study may provide insights into the mechanisms underlying CIR and offer novel therapeutics alternatives for relapse to drug use in human addicts.

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**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

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**Program#/Poster#:** 515.10/SS28

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Psychological and metabolic effects of naltrexone in rats

**Authors: *H. M. MURPHY**[1], C. H. WIDEMAN[2]
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**Abstract:** Recently, medical methodologies related to palliative care, as well as chronic pain management, have changed in the United States. Correlating with these therapies is a rapid increase in narcotic prescriptions such as methadone, oxycodone, and hydrocodone. The primary effect of these drugs is analgesia as a direct outcome of opioid receptor binding within the central nervous system. Additionally, they have high potency in regard to stimulation of the mesolimbic pathway within the brain. Naltrexone is a synthetic opioid antagonist of the μ and κ receptors which is utilized as both an agent for pain management and as an antinarcotic abuse therapy. A related function of the drug is to help balance the immune system through its interactions with the endorphins. Given the mechanism of action of naltrexone on the mesolimbic pathway, an important consideration is the potential for the drug to elicit an anxiogenic effect. In the current study, a rat model was used to assess potential psychological and metabolic effects of naltrexone. Anxiety effects of the drug were tested employing the elevated plus maze (EPM), while metabolic effects were ascertained through the measurement of food intake, water intake, and body weight gain. Twelve Long-Evans female rats were divided into two groups, control (n=6) and naltrexone-treated (n=6). Rats were exposed to a 12h:12h light-dark cycle and drug administration was implemented at the beginning of the dark period. Naltrexone-treated rats were given a 2mg/kg dose of the drug as a solution within a condensed milk “treat” and control rats were administered water dissolved in condensed milk. The experiment was divided into five weeks, composed of one habituation week and four experimental weeks. EPM testing was performed on the last day of the habituation week and following drug administration on the last day of each test week. Time spent in the open and closed arms was utilized for assessment of anxiety. Results indicated that there were no significant effects on anxiety, body weight, or food intake. A significant difference in water intake was observed between the groups suggesting that naltrexone induces increased thirst. The effect on water intake may be explained by the function of μ opioid receptors on renal function in the peripheral nervous system. Should the findings of the present study transition to human patients, the lack of deleterious side effects significantly enhances the clinical efficacy of the drug. Considering the widespread and unpleasant nature of

chronic pain and drug addiction, naltrexone may serve as a valuable pharmacological agent in palliative care, pain management, and opioid drug abuse therapy.

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**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** the Youth 1000 Talent Program of China

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**Title:** 10-days 20 hz repetitive magnetic stimulation (rtms) recovered functional connectivity in chronic smokers: A pilot study

**Authors: Z.-W. SHEN, 310005**[1], D. CHANG[1], W. PENG[1], J. ZHANG[1], Q. GE[1], X. GAO[1], Y. JING[1], Y. DU[1], Z. ZHAO[1], A. R. CHILDRESS[2], *Z. WANG[1]
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**Abstract: Aims:** Chronic smoking/nicotine dependence has been shown to have reduced functional connectivity (FC) especially in the prefrontal brain. Directly modulating brain activity in frontal cortex may help recover FC and improve the long-term smoking cessation rate. The purpose of this study is to examine whether FC in chronic smokers can be improved by high-frequency beneficial repetitive transcranial magnetic stimulation (rTMS) and whether that improvement is associated with smoking cessation. **Methods:** 14 treatment-seeking smokers (>10 cigarettes per day, Fagerstrom score>5, years of smoking>8, times of quitting attempts>3) were recruited for 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 target 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. Resting state fMRI (rsfMRI) was collected at the baseline and T10. FC was calculated from rsfMRI after data preprocessing using standard routine. **Results:** Ten smokers finished the entire treatment program. 9 didn't smoke during the entire 35 days; one relapsed because of non-cooperation. Withdrawal and craving were the same after T10 and F25, both were significantly

($p<0.05$) reduced compared to baseline. Two subjects were successfully followed up for 6 months and were able to keep abstinence. Only 5 subjects finished two rsfMRI scans. As compared to baseline, T10 showed increased FC ($p<0.01$, cluster>150) among frontal brain regions including prefrontal cortex, dorso-lateral prefrontal cortex, rostral/subgenual anterior cingulate cortex (ACC)/medial orbital frontal cortex, amygdala, ventral striatum, basal ganglia, insula, and dorsal ACC. Increased FC was correlated with withdrawal reduction. **Conclusions**: 20 Hz rTMS increased frontal brain FC, which is accompanied by a high smoking cessation rate. These pilot findings need further confirmation, both with 'sham' stimulation and larger sample size.

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**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH DA041480

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NARSAD

**Title:** Model-free and model-based reinforcement learning in addiction-related behaviors

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**Abstract:** Substance-dependent individuals have difficulties making adaptive, flexible decisions. These decision-making problems may be due to disruptions in reinforcement learning. A large body of work indicates that model-free (MF) learning is disrupted in substance-dependent individuals and in animals exposed to drugs of abuse, but emerging evidence suggests that model-based (MB) learning may also be impaired. It is unclear, however, if these disruptions are a consequence of chronic drug use or are a pre-existing vulnerability for developing an addiction. To address this question, we developed a rodent version of a multi-stage decision-making (MSDM) task. Long-Evans rats were trained to make decisions between two options in each of two successive trial stages. In the first stage, rats are presented with two levers and can respond on a single lever to illuminate two noseports. Responses on one lever result in the illumination of noseports A and B on 70% of trials and noseports C and D on 30% of trials, whereas these

transition probabilities were reversed for the other lever. In the second stage, rats respond to one of the two illuminated noseports to receive probabilistically delivered rewards. Trial-by-trial choice data was analyzed using a logistic regression to quantify the degree of MF and MB reinforcement learning each individual rat used in the MSDM. Rats were trained on the MSDM before and after they were trained to self-administer methamphetamine (or saline). Individual differences in MF, but not MB, reinforcement learning prior to any drug use predicted the rate of escalation in drug-taking behaviors ($R=-0.37$; $p=0.03$). The relationship between MF learning and future drug-taking behaviors was mediated by the degree to which rats used positive, but not negative, outcomes to guide their decision-making ($R=-0.44$; $p=0.01$). Following the self-administration, there was a significant disruption in both MF and MB processes in rats who had self-administered methamphetamine ($p=0.02$). These drug-induced impairments were due to disruptions in the ability of rats to use negative outcomes to guide their choice behavior ($p=0.01$). These data indicate that rats, similar to humans, use both MF and MB strategies to guide their decision-making processes and that specific components in reinforcement-learning strategies may be involved in dissociable aspects of drug addiction. Ongoing studies are examining the neural circuitry and biochemical systems underlying MF and MB strategies. By using a translationally analogous task, our study provides novel insights into the biobehavioral processes that influence the emergence and persistence of addiction-related behaviors.

**Disclosures: S.M. Groman:** None. **B. Massi:** None. **S. Mathias:** None. **D. Lee:** None. **J. Taylor:** None.

**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 515.13/SS31

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Medication Development Program Funds, NIDA/IRP

NIDA/IRP

**Title:** Exploring the neurochemistry of novel dopamine uptake inhibitors structurally related to Modafinil in Swiss-Webster mice

**Authors: *J. KEIGHRON**, M. COGGIANO, J. QUATERMAN, A. DIXON-GLEAVES, J. CAO, R. SLACK, A. H. NEWMAN, G. TANDA
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**Abstract:** Modafinil and its R-enantiomer have been evaluated as potential pharmacotherapies for treatment of psychostimulant use disorders. However, though positive clinical results have

been observed in subpopulations of cocaine addicted subjects, several clinical trials in cocaine and methamphetamine addicted individuals have failed to support the use of modafinil as a pharmacotherapeutic in this patient population. Novel dopamine uptake inhibitors, structurally related to modafinil, have been designed and synthesized to improve the potential therapeutic effects of their parent drug. These novel analogues, JJC8-016, JJC8-088, JJC8-089, and JJC8-091, in addition to having structural similarities to modafinil bind to the dopamine transporter with affinities similar to or higher than either modafinil or cocaine. Interestingly, like the parent drug, these novel dopamine uptake inhibitors do not produce typical cocaine-like effects in vivo. In this study, we show the effects of these compounds in Swiss-Webster mice on behavioral activity (distance travelled in an open field), tonic (microdialysis) and phasic (Fast Scan Cyclic Voltammetry, FSCV) dopamine changes in the accumbens shell, and calcium mobilization (using fiber photometry procedures). To date, our results show that several of these novel modafinil analogues function as atypical dopamine uptake inhibitors, in agreement with atypical effects shown by their parent compound (Loland et al., Biol. Psychiatry 2012). For instance, they produce little effect on distance travelled or on phasic dopamine output alone compared to cocaine. Furthermore, when given in combination with cocaine they attenuate its effects on phasic efflux of dopamine in mouse nucleus accumbens shell. Characterization of the effects of these compounds on the dopamine system provides mechanistic insight into the design of future medications for the treatment of psychostimulant use disorders.

**Disclosures:** **J. Keighron:** None. **M. Coggiano:** None. **J. Quaterman:** None. **A. Dixon-Gleaves:** None. **J. Cao:** None. **R. Slack:** None. **A.H. Newman:** None. **G. Tanda:** None.

**Poster**

**515. Treatment Mechanisms for Substance Use Disorders**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 515.14/SS32

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** R44DA035051

**Title:** Pharmacological evaluation of potential therapeutics on smoking cessation: behavioral and computational analyses

**Authors: *Q. CHANG**, W. MIN, A. C. HACKETT, M. T. LANG, M. BANSAL, T. HANANIA
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**Abstract:** This project evaluated the utility of various reference compounds with diverse mechanisms of action as potential treatments for smoking cessation using drug discrimination (DD) and nicotine self-administration (SA) tests. We screened eighteen compounds alone or in combinations to evaluate their efficacy in smoking cessation. Using bioinformatics analysis on

these behavioral data we ranked each compound based on its relative effectiveness and calculated its efficacy score. Our results identified Cytisine (an α4β2 receptor agonist) at 3 mg/kg, bPiDI (an α6β2 receptor agonist) at 3 mg/kg and the combination of Metyrapone (a corticosteroid synthesis blocker, 12.5 and 25 mg/kg) and Oxazepam (a benzodiazepine, 5 and 10 mg/kg) to be efficacious in disrupting nicotine discrimination. In the self-administration assay, Baclofen (a $GABA_B$ agonist) 3 mg/kg, BHF 117 (a $GABA_B$ receptor modulator) 30 mg/kg and MTEP (a mGlu5 antagonist) 3 mg/kg significantly attenuated nicotine self-administration. In addition, being ACh receptor agonists, both Cytisine (3 mg/kg) and bPiDI (3 mg/kg) attenuated nicotine self-administration and showed efficacy in substituting for nicotine in DD model. Put together, our studies identified, among the compounds we have studied, Cytisine and bPiDI to be the best candidates for smoking cessation. Both these compounds displayed efficacy in substituting for nicotine in DD model, caused disruption of nicotine DD as well showed efficacy in suppressing nicotine self-administration. The efficacies of combinations of Metyrapone and Oxazepam, as well as Baclofen, BHF 177 and MTEP will needs to be further evaluated due to their strong efficacy in suppressing nicotine DD or nicotine SA, respectively. *(This project was sponsored by NIDA Grant R44DA035051. We thank Dr. Neil Paterson and Dr. Daniela Brunner for their help during the studies.)*

**Disclosures: Q. Chang:** None. **W. Min:** None. **A.C. Hackett:** None. **M.T. Lang:** None. **M. Bansal:** None. **T. Hanania:** None.

**Poster**

**516. Regulation of Ethanol Intake**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 516.01/SS33

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Exercise induced escalation of alcohol intake is modulated via BDNF/TrkB

**Authors: *A. THORSELL**
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**Abstract:** Cross-sensitization is a phenomenon that occurs when drugs acting on the same pathways potentiate or sensitize a behavioral response. This is well-established for drugs of abuse, and increasing evidence indicates that it also occurs for other behaviors, for example sugar intake and exercise. Exercise is psychologically beneficial and leads to positive changes in mood as well as decreased levels of anxiety. ‘Runners high’ which is often experienced immediately after a exercise can be regarded as a state of euphoria, and involves neurobiological substrates regulating reward. The beneficial effects of exercise in the brain are accompanied by an increase in BDNF, a trophic factor associated with cognitive improvement, as well as alleviation of anxiety and depression. Exercise-induced BDNF-expression may be regulated by a

naturally occurring ketone-body, beta-hydoxybutyrate. Beta-hydroxybutyrate induces activity at Bdnf promoters, particularly the activitity dependent promoter I. Here, we examine cross-sensitization between exercise and alcohol in mice. Furthermore, we evaluate the role of BDNF and its receptor, TrkB, in mediating this effect. Mice (C57Bl6, male) were used in all studies. In the first experiment, animals were given access to a running wheel for three weeks followed by behavioral testing (elevated plus-maze, forced swim test, locomotion) and voluntary alcohol intake. In experiment two, animals were given access to a TrkB agonist, 7,8-dihydroxyflavone, or beta-hydroxybutyrate, in their drinking water for three weeks followed by behavioral evalutation. Alterations in BDNF and TrkB levels were evaluated as gene expression changes by realtime-PCR. Exercise in the form of running wheel access increased voluntary alcohol consumption in a two-bottle choice model (at 15% alcohol: exercise: 17.2 ± 0.8 g/kg BW/24hrs; Controls: 13.3 ± 0.7 g/kBW/24hrs; $p<0.01$). Additionally, an anxiolytic-like effect was seen as measured by increased open arm exploration in the elevated plus-maze (Exercise: 26.0 ±.2.7% open arm time; Controls: 15.1 ± 2.8%; $p>0.01$). However, we were unable to reproduce previously shown anti-depressant effects of exercise. Intake of 7,8-dihydroxyflavone or Beta-hydroxybutyrate also lead to subsequent elevation of alcohol-intake, as well as having both anxiolytic and antidepressant effects. Exercise strongly activated BDNF/TRkB in the hippocampus and amygdala, as indicated by elevated gene expression in these regions. In conclusion, we here demonstrate cross-sensitization between exercise and alcohol. This may be mediated by activation of the BDNF/TrkB in brain-areas such as the amygdala.

**Disclosures: A. Thorsell:** None.

**Poster**

**516. Regulation of Ethanol Intake**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 516.02/SS34

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIAAA Division of Intramural Clinical and Biological Research

**Title:** Self-initiated operant ethanol administration in male C57Bl/6j mice

**Authors: *K. P. ABRAHAO**[1], D. M. LOVINGER[2]
[1]Laboratoy of Integrative Neurosci., [2]Chief, Lab. Integrative Neurosci, NIAAA/NIH, Rockville, MD

**Abstract:** Operant conditioning is a learning process in which a new behavior is learned through reward. Mice can be trained to lever press for rewards such as drugs of abuse, and presentation of discriminative cues can foster this learning. However, there are few studies of self-initiated (i.e. cue-independent) “free-operant” responding for ethanol. Although tastant fading procedures

have been used, the initial learned association is not between the mouse's action and ethanol, but between the action and sucrose, saccharin or monosodium glutamate. Therefore**,** it would be advantageous to develop a free-operant paradigm in which the initial learned association is between lever pressing and ethanol. By incorporating aspects of drinking-in-the-dark, intermittent two-bottle choice, and chronic intermittent ethanol exposure procedures, we have been developing an operant self-administration paradigm with levers continuously available**,** no discriminative cues and no requirement of tastant fading. We used overnight intermittent training on a fixed ratio 1 (FR1) schedule for several nights to establish lever pressing levels for water or 10% ethanol. Mice were then moved to an FR3 schedule. The total presses were higher in mice self-administrating ethanol when compared to mice pressing for water. Mice were moved to a contingency degradation (CD) schedule, with water or ethanol delivered at random intervals with no contingency to the lever press. Mice in the ethanol group escalated their lever pressing in the CD condition and showed higher lever pressing rates compared to the water group. When mice were moved back to the FR3 schedule, lever pressing in the water group returned to levels seen during the previous FR3 training nights. In contrast, animals in the ethanol group retained higher lever pressing rates in comparison to the previous FR3 session. In a second experiment, we have been investigating if the outcome-independent self-initiated pressing for ethanol is dependent on the activity of the dorsolateral striatum, a brain region implicated in habitual behavior. We are using Gi coupled Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to inhibit the activity of medium spiny neurons in the dorsolateral striatal. Our findings to date indicate that ethanol promotes outcome-independent self-initiated actions exceeding those driven by another reinforcer (water), and that water-seeking animals can re-establish contingent behaviors while ethanol-seeking mice retain escalated responding. This methodology for self-initiated operant ethanol administration may be useful for examining the neural mechanisms of habitual ethanol seeking behavior.

**Disclosures: K.P. Abrahao:** None. **D.M. Lovinger:** None.

**Poster**

**516. Regulation of Ethanol Intake**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 516.03/SS35

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** European Union's Horizon 2020 research and innovation program (668863, SyBil-AA)

**Title:** Effects of chemogenetic activation and inhibition of the nucleus accumbens and insula neurons on alcohol drinking in rats

**Authors: M. HAARANEN**[1], S. HAKLI[1], S. IDRISS[1], *P. HYYTIA[2,1]
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**Abstract:** Using neuroimaging, we have previously shown that the nucleus accumbens and connecting brain regions, including the insular cortex, are activated during voluntary alcohol drinking in rats. The nucleus accumbens is a key structure involved in mediating motivational and emotional processes, whereas the insula is implicated in interoceptive effects and decision making during goal-directed actions. In order to elucidate the role of these brain regions in the regulation of alcohol drinking further, we used viral-mediated gene transfer of designer receptors exclusively activated by designer drugs (DREADDs) to either activate ($G_q$-DREADD, AAV8-hSyn1-hM3D($G_q$)-mCherry) or inhibit ($G_i$-DREADD, AAV8-hSyn1-hM4D($G_i$)-mCherry) neurons in the nucleus accumbens and insula. We trained alcohol-preferring AA (Alko, Alcohol) rats to drink 10% (v/v) alcohol during 2-h sessions every second day (Mondays, Wednesdays, Fridays) with tap water as the alternative fluid. Once the rats achieved stable baseline drinking, we anesthetized them with isoflurane and microinjected the DREADDs bilaterally (0.75 µl/side) into the nucleus accumbens core or anterior insular cortex. Four weeks were allowed for DREADD expression to accumulate before clozapine-N-oxide (CNO) testing. CNO (10 mg/kg, i.p.) was injected 60 min prior to the 2-h limited access drinking session. At the conclusion of the experiments, we deeply anesthetized the rats with pentobarbital and perfused them transcardially. The expression of DREADDs was verified from coronal brain sections by immunohistochemistry. Silencing the accumbens neurons with the $G_i$-DREADD significantly decreased alcohol drinking, whereas activation with the $G_q$-DREADD tended to increase alcohol intake. No significant effects on alcohol drinking were seen in the EGFP-expressing control group, and none of the DREADDs affected water intake. In contrast, when expressed in the insula, the activating $G_q$-DREADD significantly decreased alcohol drinking. The $G_i$-DREADD and EGFP-expressing groups displayed no changes in alcohol intake, but water intake was slightly increased in all three AAV vector groups. These results provide further evidence that both the nucleus accumbens and insula belong to the intricate forebrain neurocircuitry underlying alcohol reinforcement and consumption. However, the effects of neural activation and suppression in the accumbens differed from those in the insula, suggesting that these brain areas have diverse functions in controlling alcohol drinking.

**Disclosures:** **M. Haaranen:** None. **S. Hakli:** None. **S. Idriss:** None. **P. Hyytia:** None.

**Poster**

**516. Regulation of Ethanol Intake**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** ISF grants 968-13 and 1916-13

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NIPI 110-14-15

**Title:** Fibroblast growth factor 2 (FGF2) in the dorsomedial striatum is a positive regulator of alcohol consumption

**Authors: *O. EVEN-CHEN**[1], Y. SADOT-SOGRIN[2], O. SHAHAM[1], S. BARAK[1]
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**Abstract:** Alcohol use disorder is a chronic relapsing disorder, characterized by preoccupation with obtaining alcohol and a narrowing of the behavioral repertoire toward excessive and compulsive alcohol consumption. Repeated alcohol intake leads to neuroadaptations in the mesolimbic and nigrostriatal dopaminergic pathways, which results in drinking escalation, and other addiction phenotypes. Fibroblast growth factor 2 (FGF2) has been shown to interact with the dopaminergic system, and has been implicated in the actions of psychostimulants in the brain, as well as in several psychiatric disorders. The aims of the present study were to **(1)** determine the responsiveness of the *Fgf2* gene to alcohol exposure in rodents; and **(2)** test the effect of recombinant FGF2 (rFGF2) administration on alcohol consumption. We found that acute alcohol exposure (2.5 g/kg, i.p.) increased the mRNA expression of *Fgf2* in the dorsal hippocampus, nucleus accumbens and dorsal striatum. Longer alcohol exposure (7 days X 2.5 g/kg, i.p.) restricted these increases to the dorsal striatum, and we show that this increase is mediated via activation of the dopamine D2 receptor. Long-term excessive voluntary alcohol consumption in the intermittent access two-bottle choice paradigm increased *Fgf2* expression selectively in dorsomedial striatum (DMS). Importantly, we found that systemic rFGF2 administration or local infusions into the dorsal striatum or the DMS led to increased alcohol consumption and preference, with no similar effects on sweetened solution (saccharin) consumption. Our results identify FGF2 as an alcohol responsive gene for the first time. Moreover, we show that FGF2 promotes excessive alcohol consumption, providing a positive regulatory feedback loop of alcohol and FGF2. Hence, our finding suggests that FGF2 may be involved in the development of alcohol use disorder.

**Disclosures: O. Even-Chen:** None. **Y. Sadot-Sogrin:** None. **O. Shaham:** None. **S. Barak:** None.

**Poster**

**516. Regulation of Ethanol Intake**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH grant AA013517

Gates Millennium Scholarship Program

University of Texas Waggoner Center for Alcohol and Addiction Research

**Title:** Rodent ultrasonic vocalizations as biomarkers of future alcohol use: A predictive analytic approach

**Authors: *C. L. DUVAUCHELLE**[1], N. MITTAL[2], W. T. MADDOX[3], T. SCHALLERT[4]
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**Abstract:** Excessive alcohol consumption has a vast, negative impact on society. Rodent models have been successful in furthering our understanding of the biological underpinnings that drive alcohol consumption. Rodents emit ultrasonic vocalizations (USVs) that are each composed of several acoustic characteristics (e.g., frequency, duration, power and bandwidth). USVs reflect neurotransmitter activity in dopaminergic and cholinergic neurotransmitter systems and thus serve as non-invasive, real-time biomarkers of dopaminergic and cholinergic neurotransmission. In the present study, we recorded spontaneously emitted USVs from alcohol-naïve Long-Evans (LE) rats and then measured their alcohol intake. We compared the USV acoustic characteristics and alcohol consumption data from LE rats with previously published data from selectively bred high- (P and HAD-1) and low-alcohol (NP and LAD-1) drinking strains from studies with the same experimental method. Predictive analytic techniques were applied simultaneously to this combined data set and revealed that: (a) alcohol-naïve USVs accurately discriminated among high-alcohol consuming, LE, and low-alcohol consuming rat lines, and (b) future alcohol consumption in these same rat lines was reliably predicted from the alcohol-naïve USV profiles. To our knowledge this is the first study to show that alcohol consumption is predicted directly from alcohol-naïve USV profiles. Because USV acoustic characteristics are sensitive to underlying neural activity, these findings suggest that rodent alcohol consumption can be predicted from differences in baseline cholinergic and dopaminergic tone.

**Disclosures: C.L. Duvauchelle:** None. **N. Mittal:** None. **W.T. Maddox:** None. **T. Schallert:** None.

**Poster**

**516. Regulation of Ethanol Intake**

**Location:** Halls A-C

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** T32AA007474-27

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VA Medical Research

**Title:** Effects of voluntary wheel running on Bdnf mRNA expression following chronic intermittent ethanol exposure in C57BL/6J mice

**Authors: *M. G. SOLOMON**[1], J. E. THOMPSON[1], R. I. ANDERSON[2], H. C. BECKER[3]
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[3]Charleston Alcohol Resch Ctr., Med. Univ. South Carolina, Charleston, SC

**Abstract:** Repeated cycles of chronic intermittent ethanol (CIE) exposure increases voluntary ethanol consumption and reduces BDNF expression in mPFC of mice. We previously demonstrated that infusion of BDNF into the mPFC of ethanol-dependent mice attenuates CIE-induced escalation of ethanol intake. Our lab has recently demonstrated 2-hr daily running for 6 weeks increases Bdnf mRNA in medial prefrontal cortex (mPFC) and hippocampus dentate gyrus (DG) of C57BL/6J mice. The present study investigates the effects of wheel running on ethanol consumption (at baseline and following CIE exposure) and Bdnf mRNA expression in several brain regions immediately following a 5$^{th}$ CIE exposure cycle. Adult male C57BL/6J mice were divided into 4 groups (N= 11/group): air exposed (AIR), air exposed with wheel (WH), CIE exposed (CIE) and CIE exposed with wheel (CIE+WH). All mice were allowed limited access (2 hr/day Mon-Fri) to 15% ethanol vs water for 6 weeks (baseline). One hour after ethanol was removed, wheel groups (WH; CIE+WH) had 2-hr access to a running wheel (7 day/week). Data collected during baseline replicates and confirms our previous findings that access to an exercise wheel increases ethanol intake compared to non-wheel running mice (Wheel: 1.56 g/kg vs. No Wheel: 1.07 g/kg; $p< 0.05$). After 6 weeks of baseline mice went through weekly cycles of CIE vapor or air exposure (16 hr/day x 4 days) alternated with drinking test weeks. Baseline ethanol intake did not alter daily wheel running, but wheel running increased daily ethanol intake as we have previously seen. Our previous results show 2-hr wheel running increases Bdnf mRNA in mPFC (~35%) and DG (~25%) at the end of baseline. As we previously observed, wheel running resulted in the attenuation of CIE-induced escalation of EtOH intake in CIE+WH group compared to CIE only mice. (CIE group: ~145% increase vs. CIE+WH group: ~50% increase over baseline ethanol intake at end of study; $p< 0.05$). Immediately following the 5$^{th}$ CIE exposure, mice were sacrificed and brains removed and dissected on ice to measure Bdnf mRNA expression by qRT-PCR. Previous and current data suggest exercise can attenuate CIE-induced escalation of ethanol drinking and this effect may be mediated by exercise-induced elevation of Bdnf mRNA expression in mPFC.

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**Poster**

**516. Regulation of Ethanol Intake**

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**Topic:** G.08. Drugs of Abuse and Addiction

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NIGMS 8 P20 GM103542-02

NIAAA AA020930

NIAAA AA024426

**Title:** Glutathione-S-transferase pi and S-glutathionylation contribute to alcohol dependence and consumption

**Authors: *J. D. UYS**[1], A. E. PADULA[3], M. F. LOPEZ[6], W. C. GRIFFIN, III[2], C. OBELLIANNE[4], D. M. TOWNSEND[5], P. J. MULHOLLAND[7]
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**Abstract:** Oxidative-nitrosative stress (ROS/RNS) is a contributing factor to neurodegeneration associated with heavy chronic ethanol consumption. Compelling recent evidence suggests that oxidative stress signaling induced by prolonged drinking not only contributes to cellular injury, but may also influences the motivational states that drive heavy ethanol consumption. Cysteine residues are under-represented in mammalian proteins, but play critical roles in protein folding, antioxidant defense, and redox signaling. ROS/RNS can modify reactive cysteine residues in proteins, which includes the redox-mediated posttranslational modification, S-glutathionylation. S-glutathionylation of cysteine residues can dynamically influence cellular functioning under pathological conditions and is catalyzed by glutathione-S-transferase Pi (GSTP). Previous work has shown that GSTP contributes to cocaine-induced sensitization behavior and may be triggered by redox signaling mechanisms which are shared by all drugs of abuse, including ethanol. The purpose of this study was to determine how chronic intermittent ethanol (CIE) exposure of C57BL/6J mice alters expression of GSTP in the nucleus accumbens core (NAcc) and if this redox-sensitive protein play a role in regulating ethanol consumption. Western blot analysis confirmed that CIE exposure significantly increased GSTP expression in the NAcc. Furthermore, using a fluorescent thiol specific probe, CIE exposure resulted in an increase in cysteine thiol modifications in the NAcc. Examination of intake levels using the drinking-in-the-dark model

revealed that mice with a genetic deletion of GSTP (GSTP KO) consumed significantly more ethanol than their wildtype (WT) littermates. The enhanced intake in the GSTP KO mice was evident during the 2 and 4 hr drinking sessions. Sucrose consumption or metabolism of ethanol (3 g/kg, ig) did not differ between WT and GSTP KO mice. Treatment with carnosic acid (25 and 50 mg/kg), increased glutathione S-transferase pi activity and decreased ethanol consumption. Together, these data demonstrate that CIE exposure of C57BL/6J mice significantly alters GSTP protein expression in the NAcc and that genetic deletion or pharmacological activation of GSTP alter ethanol intake.

**Disclosures: J.D. Uys:** None. **A.E. Padula:** None. **M.F. Lopez:** None. **W.C. Griffin:** None. **C. Obellianne:** None. **D.M. Townsend:** None. **P.J. Mulholland:** None.

**Poster**

**516. Regulation of Ethanol Intake**

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**Program#/Poster#:** 516.08/SS40

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** PDSE 99999.009920/2014-05

ZIA-AA000421

**Title:** Lack of LRRK2, a Parkinson’s disease-related protein, promotes compulsive-like and high alcohol intake in mice

**Authors: D. DA SILVA E SILVA**[1], A. B. GODARD[2], *V. A. ALVAREZ[1]
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**Abstract:** Chronic alcohol exposure alters striatal function and drives action selection towards the compulsive alcohol-seeking despite negative consequences. This behavioral progression from the controlled alcohol use to compulsion is a hallmark of alcohol use disorders and its molecular mechanisms underlying is still unknown. The striatum plays a central role in goal-directed behaviors and addiction, and it is a well-defined substrate to long-lasting molecular and morphological changes evoked in addiction. In order to elucidate the molecular components behind the compulsive alcohol consumption, we evaluated the whole striatal transcriptome of a mouse model of chronic and voluntary ethanol drinking. In this model, outbred mice had simultaneous access to ethanol and water during four stages: Acquisition (alcohol and water access), Withdraw (only water access), Re-exposure (alcohol and water access) and Adulteration (water and quinine-adulterated ethanol solution). Animals were then classified according to their individual alcohol consumption pattern as "Light drinkers" (preference for water throughout

experiment), "Heavy drinkers" (preference for ethanol, but significantly reduction on ethanol intake during taste-adulteration) and "Inflexible drinkers" (preference for ethanol, even after the taste-adulteration). Aversion-resistant alcohol intake in mice has been considered to model compulsive aspects of alcohol consumption in humans. Following the transcriptome analysis, we found that the Lrrk2 gene was upregulated only in animals of the Inflexible drinkers group which show compulsive-like ethanol intake. This gene product is an AKAP protein that regulates the PKA availability in striatal neurons and affect several neuronal process and functions. Further studies showed that Lrrk2 knockout mice (Lrrk2-KO) have enhanced alcohol preference and consumption compared to wild types. Furthermore, Lrrk2-KO mice exert higher effort to gain access to ethanol solution in an operant task during progressive responding ratio schedule, indicating an increased motivation to both seek and take alcohol. In addition, similarly to the “Inflexible drinkers”, Lrrk2-KO mice showed compulsive-like ethanol consumption and maintained high ethanol intake despite pairing with an aversive taste. Taken together, these findings support the hypothesis of the LRRK2 protein is a key substrate involved in regulating alcohol consumption and the transition to compulsive, uncontrolled alcohol intake.

**Disclosures:** **D. da Silva e Silva:** None. **A.B. Godard:** None. **V.A. Alvarez:** None.

**Poster**

**516. Regulation of Ethanol Intake**

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**Program#/Poster#:** 516.09/SS41

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Swedish research council

**Title:** A molecular mechanism for choosing alcohol over a natural reward in rats

**Authors: *E. AUGIER**[1], E. D. BARBIER[2], R. DULMAN[3], G. AUGIER[1], E. DOMI[1], R. BARCHIESI[1], M. HEILIG[1]
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**Abstract:** Once established, alcohol addiction is a chronic relapsing disorder, in which alcohol use becomes compulsive, i.e. continues despite negative consequences. Understanding the transition from controlled to compulsive alcohol use is therefore a critical challenge for addiction research. In humans, only a subset of users transition to compulsive drug use. In contrast, in commonly used animal models, nearly all rats learn to self-administer addictive drugs, including alcohol. This observation points to the possibility that focusing on self-administration alone may be insufficient to identify key mechanisms of addiction. This realization has prompted some

important conceptual advances. For instance, it has been found that most rats will seize to self-administer cocaine when a high-value alternative becomes available, but that a subset of animals will continue their self-administration despite the presence of an alternative. The neurobiological underpinnings of choosing alcohol over a natural reward are presently largely unknown. Here, we set out to identify molecular mechanisms underlying this choice behavior. We first established an exclusive choice-based method to identify rats that continue to self-administer alcohol at the expense of a high-value natural reward, a sweet solution, and assessed whether these animals show other characteristics reminiscent of clinical alcoholism. We then carried out a discovery effort using gene expression profiling, and identified a novel molecular mechanism that appears to mediate compulsive-alcohol drinking at the expense of other high-value options.

**Disclosures:** **E. Augier:** None. **E.D. Barbier:** None. **R. Dulman:** None. **G. Augier:** None. **E. Domi:** None. **R. Barchiesi:** None. **M. Heilig:** None.

**Poster**

**516. Regulation of Ethanol Intake**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 516.10/SS42

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant AA025244

**Title:** Role of the transcriptional regulator LMO4 in excessive alcohol consumption

**Authors: R. MAIYA**, *R. O. MESSING
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**Abstract:** Repeated alcohol exposure leads to changes in gene expression that are thought to underlie the transition from moderate to excessive drinking. Gene expression profiling studies have identified a multitude of ethanol-responsive gene networks, but the mechanisms by which these networks are mobilized to a neuroadaptive response are not well understood. One mechanism could involve ethanol regulation of transcriptional co-regulators that bind and modulate the activity of several transcription factors, thereby orchestrating a diverse neuroadaptive transcriptional network. Our results indicate that the transcriptional regulator LMO4 is one such candidate regulator. Mice harboring a gene trap insertion at the *Lmo4* (*Lmo4gt/+*) locus consumed significantly more ethanol and showed enhanced preference for ethanol in a 24-hour intermittent access procedure. Ethanol intake was not significantly different between the two genotypes in a 4-h, limited, intermittent access procedure and in a standard 24-h, continuous access, two-bottle choice procedure. Two-bottle choice sucrose, saccharin, and quinine preference were also not different between the genotypes. Further, LMO4 levels in the nucleus accumbens decreased during intermittent, binge-like ethanol consumption but not during

continuous access ethanol consumption. Knockdown of LMO4 in the nucleus accumbens (NAc) by RNA interference significantly enhanced alcohol consumption without affecting water, sucrose or quinine consumption. We also examined the effects of LMO4 knockdown in the BLA, a brain region where LMO4 functions to regulate cue-reward and fear learning. Surprisingly, knockdown of LMO4 in the basolateral amygdala (BLA) significantly reduced alcohol consumption and preference. Experiments are currently underway to determine whether LMO4 knockdown in these brain regions affects the development of conditioned place preference to ethanol and also to examine transcriptional targets of LMO4 in the NAc and the BLA. In summary, our findings lead to us to conclude that LMO4 is an ethanol-responsive, transcriptional co-regulator that differentially regulates excessive alcohol consumption in a brain region-specific manner. Supported by NIH grant AA025244.

**Disclosures: R. Maiya:** None. **R.O. Messing:** None.

**Poster**

**516. Regulation of Ethanol Intake**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 516.11/SS43

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH T32 NS007431

NIH KO1 AA023555-01

**Title:** A role for neurotensin hindbrain-projecting central nucleus of the amygdala neurons in alcohol drinking and reward

**Authors: *M. L. TORRUELLA SUAREZ**[1], J. VANDENBERG[2], J. A. HARDAWAY[3], E. S. COGAN[2], J. D. DIBERTO[2], T. L. KASH[4], Z. A. MCELLIGOTT[3]
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**Abstract:** Alcohol use engages a number of different circuits, including those involved in anxiety and reward. Our data suggests that a neurotensin-containing (NTS+) central amygdala (CeA) projection to the parabrachial nucleus (PBN) plays a role in modulating ethanol consumption and reward behaviors. Using genetically- and virally driven caspase-3 in male NTS-Cre mice, we show that ablation of these neurons resulted in decreased ethanol drinking in both a 2 bottle choice paradigm and in an intermittent access paradigm, without concurrent changes in measures of anxiety.
Moreover, using a Ce-dependent optogenetic approach in our NTS Cre mice we have targeted PBN-projecting NTS+ neurons in the CeA with channelrhodopsin. Mice show a preference for

stimulation in a real-time place preference assay, and will nose-poke for intracranial stimulation of this projection. Stimulation of this projection also promotes ethanol drinking. This data together suggests that this long-distance GABAergic projection is rewarding and plays a role in the reinforcement of ethanol consumption.

**Disclosures: M.L. Torruella Suarez:** None. **J. Vandenberg:** None. **J.A. Hardaway:** None. **E.S. Cogan:** None. **J.D. DiBerto:** None. **T.L. Kash:** None. **Z.A. McElligott:** None.

**Poster**

**516. Regulation of Ethanol Intake**

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**Program#/Poster#:** 516.12/SS44

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH grant AA022048

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NIH grant DA00724426

**Title:** Viral vector mapping of GABAergic projections stemming from the CeA in vgat-ires-cre and NPY1R-cre mice

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**Abstract:** Central amygdala (CeA) GABAergic neurons have been shown to play a key role in modulating binge ethanol (EtOH) consumption. GABAergic neurons in the CeA co-release corticotropin-releasing factor (CRF) and express neuropeptide Y1 receptors (NPY1R). First, a Cre-dependent channelrhodopsin viral vector was injection into the CeA of vGat-ires-cre mice on a C57BL/6J background and was used to map GABAergic projections originating from this region. Animals were allowed to remain in home change for about 2 months in order to allow incorporation and spread of the viral vector. We then perfused animals with a 4% paraformaldehyde solution in order to fix tissue and sliced utilizing a vibratome. Every other slice of each brain was mounted and cover-slipped in order to map out projections from these regions. Many expected projections were seen to areas known to be associated with drugs of abuse. A novel GABAergic project from the CeA was to a specific location within the LHb. This same technique was used with an NPYR1-cre line in order to map out projections specifically from the CeA. This mapping analysis also revealed similar projections stemming from the CeA, including a project to the LHb, which is consistent with the hypotheses that GABAergic neurons in this pathway express Y1R. The lateral habenula (LHb) has been shown to play a role in the

negative affective states of drug use including those associated with EtOH. In order to investigate this specific pathway our lab is currently utilizing chemogenetic inhibitory ($G_{i/o}$) and excitatory ($G_q$) Designer Receptors Exclusively Activaed by Designer Drug (DREADD) viral vector technology injected into the CeA while simultaneously cannulating the LHb. This work was supported by NIH grants R01 AA022048, R01 AA013573, and, T32 DA00724426.

**Disclosures: M.A. Companion:** None. **T.E. Thiele:** None.

**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 517.01/SS45

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Center for Brain and Behavior Research Pilot Grant

South Dakota Governor's Team Development Grant

**Title:** Neural and psychological characteristics of college students with alcoholic parents differ depending on current alcohol use

**Authors: *J. L. SCHOLL**[1,2], K. A. BROWN-RICE[3,2], K. A. FERCHO[1,2], K. PEARSON[3,2,1], N. A. KALLSEN[4], G. E. DAVIES[4], E. A. EHLI[4], S. OLSON[3], A. SCHWEINLE[3,2], L. A. BAUGH[1,2], G. L. FORSTER[1,2]
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**Abstract:** A significant proportion of college students are adult children of an alcoholic parent (ACoA), which can confer greater risk of depression, poor self-esteem, alcohol and drug problems, and greater levels of college attrition. However, some ACoA are resilient to these negative outcomes. The goal of this study was to better understand the psychobiological factors that distinguish resilient and vulnerable college-aged ACoAs. To do so, scholastic performance and psychological health were measured in resilient (not engaged in hazardous alcohol use) and vulnerable (currently engaged in hazardous alcohol use) ACoA college students. Neural activity (as measured by functional magnetic resonance imaging) and cortisol reactivity in response to performing working memory and emotion-based tasks were assessed. Furthermore, the frequency of polymorphisms in candidate genes associated with substance use, risk taking and stress reactivity were compared between resilient and vulnerable groups. College ACoAs currently engaged in hazardous alcohol use reported more anxiety, depression and posttraumatic stress symptoms, and increased risky nicotine and marijuana use as compared to ACoAs resistant to problem alcohol use. Vulnerable and resilient ACoAs were also distinguished by distinct

patterns of activity across the brain in response to visual working memory and emotional processing tasks, particularly in the posterior cingulate. Preliminary findings suggested that polymorphisms of cholinergic receptor and the serotonin transporter genes play a role in risk determination for ACoAs. Overall, findings point to several important psychobiological variables that distinguish ACoAs based on their current alcohol use that may be used in the future for early intervention.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 517.02/SS46

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Maternal separation reduced prenatal ethanol-induced changes in hyperactivity and extracellular signal-regulated kinase activity

**Authors: *P. C. SWART**, V. A. RUSSELL, J. J. DIMATELIS
Human Biol., Univ. of Cape Town, Cape Town, South Africa

**Abstract:** Children with fetal alcohol spectrum disorders (FASD) face further adverse childhood experiences when living with alcohol-abusing parents. However, the effect between alcohol exposure *in utero* and childhood adversities on the developing brain has not been fully investigated. Hence, combining prenatal-alcohol exposure (PAE) and early-life stress in an animal model may better represent the aetiology of FASD and the associated-behavioural deficits.
Ethanol-dams voluntarily consumed a 0.066% saccharin-sweetened 10% ethanol (EtOH) solution throughout gestation while control-dams had *ad libitum* access to a 0.066% saccharin (sacc) solution. In addition, whole litters were randomly assigned to undergo maternal separation (MS) for 3 h/day from postnatal day (P) 2 to P14 while the remaining litters were left undisturbed (nMS). This resulted in 4 experimental groups: *control* (sacc+nMS), *MS* (sacc+MS), *EtOH* (EtOH+nMS) and *EtOH+MS*. Male rats were used in behavioural tests of learning and memory, as well as anxiety- and depression-like behaviour from P57 - P62. The prefrontal cortex (PFC) and dorsal hippocampus (DH) from non-behavioural male and female rats were used in western blot analysis of extracellular signal-related kinase (ERK) and glycogen synthase kinase-3β (GSK3β).
EtOH rats had reduced body mass compared to control rats. However, EtOH+MS rats tended to have a greater body mass than EtOH rats. Further, MS and EtOH rats were hyperactive during

habituation to the novel object test arena but EtOH+MS rats displayed similar activity levels to that of control rats. MS, EtOH and EtOH+MS rats had an increased number and average duration of 22 kHz ultrasonic vocalizations compared to control rats.
In adult male and female rats there was a significant interaction between PAE and MS on P-ERK/ERK in both the PFC and DH. P-ERK/ERK tended to be greater in MS rats compared to control rats whereas P-ERK/ERK tended to be lower in EtOH+MS rats versus EtOH rats. Further, PAE increased P-GSK3β in the PFC of male rats and increased P-GSK3β/GSK3β in the PFC of female rats.
A FASD-like phenotype was observed in rats exposed to prenatal-ethanol (reduced body mass, hyperactivity and a negative affective state). Importantly, P-ERK/ERK was increased in the PFC and DH after PAE. P-GSK3β and P-GSK3β/GSK3β were also increased by PAE in the PFC. Activation of the ERK signalling cascade with simultaneous *inactivation* of the GSK3β signalling pathway may have contributed to the FASD-like phenotype. MS reduced the hyperactivity in EtOH rats and decreased P-ERK/ERK in the PFC and DH. These results suggest that activation of the ERK signalling pathway plays a role in PAE-induced changes in behaviour.

**Disclosures:** **P.C. Swart:** None. **V.A. Russell:** None. **J.J. Dimatelis:** None.

**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

**Location:** Halls A-C

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**Program#/Poster#:** 517.03/SS47

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant R01 AA013983

**Title:** A murine model of female aggression: Escalation of aggressive behavior by ethanol and benzodiazepines

**Authors: *J. F. DEBOLD**[1], M. B. BICAKCI[1], E. L. NEWMAN[1], M. S. LAUZE[1], A. M. CASTANER[1], K. A. MICZEK[1,2]
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**Abstract:** Levels of violent crime committed by women have increased, particularly under the influence of alcohol. Estimated annual costs of violent crime alone in the United States exceed three billion dollars. However, a viable animal model for female aggressive behavior has not yet been characterized. Here, we use an ethologically valid model to characterize aggressive interactions in female mice. We aim to explore sex differences in the behavioral profile, and the extent to which alcohol and benzodiazepines augment aggression. Ovariectomized CFW female mice were taught to self-administer a dose of ethanol known to promote aggression in some male mice (1.0 g/kg) and assessed for the presence of alcohol-heightened aggression. Low doses of the

benzodiazepine midazolam (0.1-1.0 mg/kg) were injected IP and females were tested for aggressive behavior in five-minute intruder interactions. Frequency and duration of resident aggressive and non-aggressive behaviors were measured and compared across conditions and across doses. A subpopulation of females (ca. 25%) show heightened aggressive behavior after alcohol consumption. Midazolam also increased aggressive behavior in resident females dose-dependently, similar to what has been demonstrated in male mice. This aggressive behavior, however, was sensitive to intruder novelty and strain. Resident females expressed the greatest levels of aggression toward novel C57BL/6J intruders. Alcohol and midazolam did not induce aggression in historically non-aggressive females. Aggression in female mice without a reproductive history is mediated in a manner similar to that of male aggression. This model can produce female residents with consistent high levels of aggressive behavior.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

**Location:** Halls A-C

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**Program#/Poster#:** 517.04/SS48

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant R01 AA013983

**Title:** Social defeat stress and escalated ethanol drinking by C57BL/6J mice: Modulation by CRF-R1 and glucocorticoid receptor antagonism

**Authors: *E. L. NEWMAN**[1], P. ANDREW[1], J. G. AULD[1], K. C. BURKE[1], B. KISBY[3], E. Y. ZHANG[1], J. F. DEBOLD[1], K. A. MICZEK[1,2]
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**Abstract:** Stressful experiences can increase ethanol (EtOH) consumption in the human population. The present work used systemic pharmacological intervention to identify critical receptor targets associated with stress-escalated drinking in mice. Male C57BL/6J (B6) mice were subjected to ten days of social defeat during which larger, outbred resident males inflicted approximately thirty bites to B6 mice in under five minutes. Ten days after the final defeat, B6 mice received continuous or intermittent two-bottle choice access to 20% EtOH (w/v) and water. During four weeks of EtOH access, defeated mice consistently consumed more EtOH than non-defeated controls. From weeks 4-8, mice received weekly doses of the CRF-R1 antagonist, CP 376,395 (CP; 0-30 mg/kg IP); the 5-alpha-reductase inhibitor, finasteride (0-100 mg/kg IP); the 11-beta-hydroxylase inhibitor, metyrapone (0-50 mg/kg IP); or the glucocorticoid receptor (GR)

antagonist, mifepristone (0-100 mg/kg IP). The highest dose of CP reduced continuous, but not intermittent EtOH intake (g/kg) in defeated mice. Periods of forced abstinence during intermittent access may reduce the potentially therapeutic effects of CP; while CRF-R1 antagonism may diminish the positive reinforcing effects of EtOH, perhaps CRF-R1 is not critical for the negative reinforcing effects of EtOH withdrawal. Mifepristone dose-dependently reduced intermittent access drinking by control animals but had no effect on continuous access. Alternating between days of EtOH access and days of forced abstinence may alter HPA-axis functioning; this may be accentuated in defeated mice, causing these animals to continue drinking despite mifepristone treatment. Finasteride and metyrapone dose-dependently reduced EtOH intake, suggesting that ineffective glucocorticoid signaling in defeated mice with intermittent access to alcohol may be associated with altered receptor expression rather than corticosterone and neurosteroid synthesis. In summary, these findings suggest that CRF-R1 antagonists may be good candidates for the selective reduction of stress-escalated voluntary drinking while GR antagonists may be more effective in reducing alcohol intake that is not escalated by social defeat stress. Future work will tease apart the role of extra-hypothalamic brain regions in stress-escalated drinking through localized infusions of CRF-R1 and R2 antagonists into the central amygdala and ventral tegmental area.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

**Location:** Halls A-C

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NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

**Title:** Adolescent ethanol exposure increases adult anxiety-like behavior: Involvement of small conductance $Ca^{2+}$-activated $K^{+}$ channels in medium-sized spiny neurons of the nucleus accumbens

**Authors:** L.-L. SHAN, J. C. CARPENTER, K. RYBCZYK, T. DEAK, ***Y. Y. MA**
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**Abstract:** Alcohol use typically begins early in adolescence, during which neurodevelopment can be interfered, increasing the likelihood of adult mental disorders such as anxiety. However, the cellular mechanisms underlying the consequences of adolescent alcohol exposure remain poorly understood. This study was designed to investigate the prolonged effects of chronic intermittent ethanol (CIE) during adolescence, compared with chronic intermittent water (CIW), on anxiety levels using the light-dark exploration test and determining the intrinsic excitability of medium-sized spiny neurons (MSNs) in the striatum by whole-cell patch clamp recordings in current-clamp mode, followed by *in vivo* and *in vitro* pharmacological manipulations. All measurements were done 3 weeks after adolescent (starting at postnatal 28 days, i.e., P28) or adult (starting at P70) CIE (4 g/kg/day, administered intragastrically under a schedule of 4 cycles of 3 days on and 2 days off) or CIW (same volume of water, administered intragastrically under the same schedule). We found that the cross-over latency from light to the dark side in adolescent CIE rats was significantly reduced relative to adolescent CIW control rats, indicating increased anxiety in rats with adolescent CIE history. Cross-over latency in adult CIE and CIW groups showed no difference from that in adolescent CIW group. In parallel, the excitability of MSNs in the nucleus accumbens (NAc), but not dorsolateral striatum (DLS), from rats with an adolescent CIE history was significantly higher than that of rats with an adolescent CIW history. Furthermore, the amplitude of the medium afterhyperpolarizations (mAHP), assumed to be mediated by small conductance (SK) calcium-activated potassium *channels*, but not the fast AHP, assumed to be mediated by large conductance (BK) calcium-activated potassium channels, was decreased specifically in the adolescent CIE group. Finally, the increased anxiety level and the increased NAc excitability in rats with an adolescent CIE history were significantly reversed by *in vivo* NAc microinjections or slice bath application of SK channel activator 1-ethyl-2-benzimidazolinone (1-EBIO); whereas *in vivo* or slice application of SK channel blocker Apamin in rats with an adolescent CIW history was able to mimic the effects of adolescent CIE treatment, *i.e.*, these CIW rats showed a significantly higher level of anxiety and increased NAc excitability. These results indicate that the high anxiety level in the adult stage after adolescent CIE is mediated by decreased function of SK channels in the NAc, which could be a target to prevent or reverse anxiety disorders induced by adolescent alcohol exposure.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** K01 AA023874

R37 AA017531

U01 AA014091

P01 AA021099

**Title:** Adolescent social isolation increases kappa opioid receptor function in the nucleus accumbens and basolateral amygdala of rats

**Authors: *A. KARKHANIS**[1], J. L. WEINER[2], S. R. JONES[1]
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**Abstract:** Chronic early life stress, such as neglect during childhood, results in increased risk for alcohol use disorders during adulthood. Similarly, rats reared in social isolation (SI) during adolescence show increased ethanol (EtOH) intake in adulthood compared to group housed controls (GH). Acute stress elevates dynorphin levels, a kappa opioid receptor (KOR) ligand, which regulates dopamine (DA). Activation of KORs inhibits DA release in the NAc and BLA. The NAc and BLA are interconnected and play integral roles in the neurobiology of stress, anxiety and reward-seeking behavior. Recent literature shows that the KOR system regulates drug seeking following chronic exposure to ethanol. In order to understand the potential underlying mechanisms driving the isolation-induced increases in EtOH intake, the effects of acute EtOH on DA in the presence and absence of nor-binaltorphimine (norBNI), a KOR antagonist, were examined in the NAc and the BLA. Moreover, the sensitivity of KORs on DA terminals was examined in NAc slices from SI and GH rats.
DA in the NAc and BLA was measured using *in vivo* microdialysis in freely moving rats that were either housed in groups (4 rats/cage) or individually (1 rat/cage) for six weeks (PD 28 – 74). After reaching adulthood, acute EtOH was administered after establishing stable DA baselines. A separate group of rats was treated with norBNI (10 mg/kg; i.p.) 24 hrs prior to EtOH challenge. To investigate the KOR system further, *ex vivo* voltammetry was used to record the effects of U50,488 (10 – 1000 nM), a KOR agonist, on DA release in NAc slices from GH and SI rats.
Baseline levels of DA were significantly lower in the NAc and BLA of SI compared to GH rats. KORs increased baseline DA levels in both NAc and BLA. The SI rats showed increased DA responses to EtOH (2 g/kg) in both NAc (200% of baseline) and BLA (280% of baseline) and this increase was significantly greater in BLA than NAc. EtOH augmented DA responses in the NAc of SI rats pre-treated with norBNI, but attenuated responses in the BLA. The inhibitory effects of U50,488 on DA release were enhanced in the NAc of SI rats suggesting that chronic stress increases the functional responsiveness of KORs.
Increased DA elevations after EtOH in both regions of SI rats are consistent with the stimulant literature, however the mechanisms behind the distinct effects of EtOH-induced DA in the presence and absence of norBNI in NAc and BLA are unclear. It is possible that KOR differences may explain in part the effects of EtOH on behaviors related to specific brain regions, for example, augmentation of DA in the NAc results in increased reinforcement, whereas augmentation in DA in the BLA may contribute to decreased anxiety.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

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**Program#/Poster#:** 517.07/SS51

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** R01AA024526

**Title:** Manipulation of fear memories as a treatment for comorbid AUD and PTSD

**Authors:** ***C. E. SMILEY**, J. T. MCGONIGAL, R. J. NEWSOM, T. VALVANO, J. T. GASS
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**Abstract:** Alcohol Use Disorder (AUD) and Post-Traumatic Stress Disorder (PTSD) are highly comorbid, with rates as high as 41-79%, and share many overlapping neural circuits. One of the critical needs in this field is the development of novel pharmacological interventions to help treat these co-occurring disorders. Furthermore, research into the sex differences of AUD/PTSD needs to be investigated since prevalence rates for AUD/PTSD comorbidity differ between males and females and this has yet to be thoroughly studied in rodent models. The current studies examined the impact of chronic intermittent ethanol (CIE) exposure on fear conditioning, extinction learning and recall, and cue induced ethanol consumption in both male and female rats. Rats were first exposed to a rodent model of PTSD using fear conditioning with an “ABA” experimental design. After fear conditioning rats were exposed to either CIE or air for two weeks. Rats were then exposed to an extinction training regimen consisting of daily sessions of 10 extinction trials using tone (conditioned stimulus) presentations only. After reaching extinction criteria, rats were exposed to an extinction recall test. Two days after the extinction recall test, a “contextual” recall test was performed in the original fear conditioning environment. It was found that CIE exposed female rats acquired fear conditioning at a faster rate compared to all other groups. However, both male and female rats exposed to CIE showed a deficit in their ability to extinguish their fear behavior with this deficit being greater in male CIE exposed rats. These extinction learning deficits were recovered when rats from both sexes were treated with the positive mGlu5 modulator, CDPPB, during extinction. Sex differences were also observed in extinction recall and alcohol consumption. For example, CIE exposure resulted in a deficit in extinction memory recall in male rats only. Additionally, exposure to fear related cues significantly increased alcohol consumption in male CIE exposed rats. These results suggest that exposure to chronic alcohol after fear learning has differential effects in males and females, and some of these effects can be prevented by modulation of mGlu5. Currently, we are exploring the ability to disrupt reconsolidation of a fear-related memory through optogenetics to prevent alcohol-induced deficits in fear behaviors. Together, these results suggest that manipulation of

fear memories, through enhanced extinction learning via mGlu5 modulation or disruption of fear memory reconsolidation, can serve as a novel approach to treat individuals who suffer from AUD/PTSD comorbidity.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant AA021951

**Title:** Genetic analysis of initial and subsequent consumption of ethanol in a large panel of BXD recombinant inbred mouse strains

**Authors: *B. C. JONES**[1], L. LU[2], M. K. MULLIGAN[2], S. A. CAVIGELLI[3], W. ZHAO[2], R. W. WILLIAMS[2], E. TERENINA[4], P. MORMÈDE[4]
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**Abstract:** Heritable differences in alcohol use disorders have been recognized for several decades. Many animal models have been employed to define genes variants and biochemical networks that predispose individuals to alcohol-related problems. This includes approach, initial consumption, change or elevation in the amount consumed, and dependence. Few animal models exist that address individual differences in initial exposure, consumption, and change following exposure. To this end, we tested female mice from 36 BXD recombinant inbred strains for initial and continuing alcohol consumption using the drinking in the dark (DID) method. All animals were between 60 and 80 days of age at the start of the study. DID follows a 4-day routine on a weekly schedule. On days 1–3 (Tues–Thurs in our case) water was removed 3h after lights out and replaced for 2h with alcohol (20% v/v from 95% EtOH). On the 4$^{th}$ day, treatment was repeated, but animals had 4h exposure. For this study, we followed this routine for five weeks. For the first 2h exposure, we observed wide variation in EtOH consumed from a low of 1.08 to 3.20 g/kg. For the first 4h exposure we observed a similar wide variation from 2.50 to 6.73 g/kg across 36 strains. The correlation for consumption between these exposures was $r = 0.69$, $p < 0.01$. Mapping of strain variation in DID for both exposures revealed the same suggestive locus near the telomere of chromosome 1. A possible candidate gene is *Gm821*, gene model 821 (NCBI). This gene is *cis*-regulated and its expression correlates with alcohol consumption *r*

>0.60, $p$ <0.01. For the 5th 4h exposure (following 5 weeks of DID), the range of consumption was 3.0 to 7.2 g/kg. The correlation between the first and fifth 4h DID was $r$ = 0.62, $p$ <0.01. For this trait, we detected suggestive loci on chromosomes 16, 18 and 19, but no strong candidate genes. In comparing the 5th 4h exposure to the 1st exposure, ten strains increased their consumption over the 5 weeks, but no strains decreased their consumption.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 517.09/SS53

**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** Voluntary oral ethanol consumption as emotional self-medication

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**Abstract:** In the early stages of drug addiction, individuals may develop a preference for a substance because of the substance's ability to reduce negative affect—the emotional self-medication (ESM) hypothesis. ESM was demonstrated in rats by exposing animals to an induction task involving reward devaluation (a downshift from 32% to 4% sucrose), followed by access to 2% ethanol and water in a 2-h, two-bottle choice preference test. Ethanol consumption increased after reward devaluation sessions in comparison to control groups either not exposed to devaluation or exposed to devaluation but given access to water. Two experiments tested the assumption that ethanol consumption increased because ethanol downregulates negative affect induced by reward devaluation. In Experiment 1, rats received access to ethanol under the same conditions that produced evidence of ESM and this was followed by a 32-to-4% sucrose downshift. Previous access to ethanol did not reduce the behavioral effects of reward devaluation. In Experiment 2, rats were first exposed to the 32-to-4% sucrose downshift, then to an ethanol preference test, and finally to the elevated plus maze. Reward devaluation significantly increased ethanol consumption, and this ESM effect increased general activity in the elevated plus-maze relative to water controls. Experiment 3 tested whether an anxiolytic

action of oral ethanol on subsequent reward devaluation would require repeated experience with reward devaluation. Animals had daily access to ethanol, immediately followed by repeated cycles of 32-to-4% sucrose downshift. Access to ethanol in the preference test reduced the effects of repeated reward downshifts relative to water controls, suggesting that previous ethanol consumption can reduce negative affect after repeated reward devaluations. Overall, these results provided limited support for the assumption underlying ESM that ethanol consumption increases after reward devaluations because ethanol reduces the ensuing negative affect. The origin of addictive behavior is often linked to the rewarding effects of drugs of abuse. The ESM hypothesis offers an alternative explanation based upon the ability of many of such drugs (e.g., ethanol) to alleviate negative affect.

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**Poster**

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**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant DA038843

**Title:** Investigating the temporal relationship between chronic mild stress and alcohol intake in rats

**Authors: *C. S. BAILEY**[1], A. K. PATTERSON, 37614[2], C. A. BRADLEY[3], S. G. MALONE[2], M. I. PALMATIER[3]
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**Abstract:** There is a substantial comorbidity between alcohol use disorders (AUDs) and anxiety-related disorders, but the directional onset and temporal nature of this interaction is not well understood. To investigate the temporal relationship between stress and alcohol consumption, we adapted a model of chronic mild stress (CMS) to a home cage alcohol drinking paradigm. We hypothesized that rats exposed to CMS would show an increase in anticipatory ethanol intake as a strategy for coping with an impending stressor. CMS was used because despair models (forced swim and social defeat) decrease anticipatory alcohol intake. Rats were randomly assigned to one of two groups (Stress, n=8 or Control, n=8), both groups had access to 10% (v/v) ethanol. The Stress group was exposed to a mild stressor (e.g., wet bedding, puddled cage, cage tilt, predator urine) in a novel cage outside the colony for 3 h each test day. Control rats were transported to a novel cage outside the colony for 3 h each test day. A red ambient light was

illuminated for 2 h before the stress/novel cage exposure as an anticipatory cue. No fluids or food were available in the stress/novel cage. Alcohol intake was recorded during 3 periods every 24 h - at 0900 ethanol and water consumption from the preceding 17 h (overnight drinking), at 1100 after transport to the stress/novel cage (anticipatory drinking), and at 1600, 2 h after rats were returned to the home cage (post-stress drinking). Stress and alcohol exposure recurred over 6 days each week for 9 weeks, on the seventh day of each week no alcohol was available and rats remained in the colony. The 3 h deprivation (during stress/novel cage housing) initially increased water intake during the post-stress drink session, but this increase declined across the first 3 weeks of testing. Ethanol intake increased after deprivation - the overnight drink on the first day of testing each week. However, initial ethanol intake levels were so low, it was not clear that rats experienced the intoxicating effects of ethanol (approx. 0.4 g/kg during anticipatory and post-stress drinks). There were no initial differences in ethanol intake, but preliminary evidence suggested that both groups increased alcohol drinking during the anticipatory period. Future studies are needed to determine if the novel cage manipulation is sufficient to produce mild stress or if access to ethanol impacted the development of the stress response.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** 3R01AA021262-03S1

**Title:** Early life stress-induced alcoholism may be overcome through novel pharmacological manipulation: Implications on behavior and neurochemistry

**Authors: *O. O. KALEJAIYE**[1,2], R. BASSEY[1,2], I. BAMIDELE[1,2], V. TIRUVEEDHULA[3], J. M. COOK[3], M. C. GONDRÉ-LEWIS[1,2]
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**Abstract:** Stress-related psychiatric disorders are positively correlated to the propensity for alcoholism. Stress is particularly detrimental to brain development when it occurs during vital neurodevelopmental stages and may severely impact emotion and reward processing centers. Maternal separation stress (MS) has recently been shown by our laboratory to induce binge alcohol drinking in adult rodents. It was postulated that one neurochemical basis for this

heightened alcohol drinking behavior could be via $GABA_A$ receptor ($GABA_AR$) upregulation. This study aims to present novel $GABA_AR$-targeted pharmacological interventions which manipulate neurochemistry to rescue aberrant behavior. 3-propoxy-carboline hydrochloride (3-PBC), a $GABA_AR$ acting compound and 3 of its isoforms, BCCt, 3-IsoPBC and Cyclo-PBC, administered at doses of 10, 20, and 40mg/kg, were utilized as drug treatments. MS was induced in Sprague-Dawley pups by their daily separation from dams starting at postnatal day (PD) 2 until PD21. During early adolescence from PD28-35, behavior was tested on elevated zero maze (EZM), open field locomotor activity (OFLA) and forced swim test (FST). The rotarod test was conducted during late adolescence. At PD60 rats were trained for alcohol drinking in an operant conditioning chamber. $GABA_AR$ modulators dose-dependently and sex-specifically attenuated MS-induced increases in distance traveled, ambulatory time, stereotypy, and time spent in the center field; behaviors consistent with hyperactivity. These findings were paralleled in the EZM which showed a reduction in risk taking behavior, exhibited by an MS-induced increased time spent in the open arms. These $GABA_AR$ modulators also attenuated MS-facilitated increased immobility in the FST, a measure of depressive-like behavior. Previously, we showed that MS induced an increase in alcohol intake and now we show that females MS rats exhibit increased alcohol intake per kg body weight when compared to males. In general, $GABA_AR$ modulators had varying degrees of efficacy on behaviors, especially in alcohol consumption, with Cyclo-PBC>3Iso-PBC>3PBC>BCCt. This study presents a compelling argument that stress experienced during early life may serve as a key indicator of binge alcohol drinking later in life. Additionally, stress may have more severe behavioral ramifications in females when compared to males thus treatment profiles may be deferentially effected. Furthermore, we show that $GABA_AR$ dysregulation in ELS may be sexually dimorphic. The translational relevance of this study points to the need for adjunctive GABA-targeted pharmacological therapies which account for gender differences in humans.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

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**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** Chronic intermittent ethanol alters hypothalamic synaptic plasticity and HPA axis hormonal, as well as behavioral responses to repeated stress

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UCLA, Los Angeles, CA

**Abstract:** Alcohol use disorders are associated with a persistently dysregulated hypothalamic-pituitary-adrenal (HPA) axis and corticotropin-releasing factor (CRF) signaling that leads to inappropriate stress responses, thereby increasing relapse susceptibility in abstinent alcoholics. Our goal is to identify the neuroadaptive mechanisms responsible for the dysregulation of the HPA axis. Using whole-cell patch-clamp recordings, we showed that stress induces a CRF-dependent depression of NMDAR function in parvocellular neurosecretory cells (PNCs) in the paraventricular nucleus of the hypothalamus (PVN), which allows for short-term potentiation (STP) of AMPAR-mediated evoked excitatory postsynaptic currents (eEPSCs) following high-frequency stimulation (HFS, 100Hz for 1sec, x4). This stress-induced STP can be evoked for several days and provides a mechanism by which the HPA axis responds adaptively to subsequent stressors. Here, we found that chronic intermittent EtOH (CIE, 30 doses, 5-6 g/kg EtOH, oral gavage) and 40 days of withdrawal decreased action potential threshold in PNCs. While the frequency and amplitude of AMPAR-mediated EPSCs were unchanged, we found that CIE increased the paired-pulse ratio and potentiated NMDAR function in PNCs. Hypothalamic CRF mRNA expression was increased in CIE rats. Interestingly, the inhibitory effect of CRF on NMDAR was absent in CIE rats. Since NMDAR and CRF play a critical role in the physiological responses to stress, we investigated the effects of CIE on PNCs in rats exposed to restraint stress. We found that HFS-induced STP was impaired in PNCs of stressed CIE rats. Loss of HFS-induced STP was also found in PNCs of stressed rats exposed to intermittent EtOH vapor for 6 weeks and 40 days of withdrawal. NMDAR inhibition by intracellular MK-801 restored stress-induced STP suggesting that the loss of CRFR1-mediated NMDAR blockade in CIE rats may prevent stress-induced STP. To relate the expression of STP to the HPA axis hormonal response, we examined ACTH and CORT plasma levels in response to repeated (at 72hr-intervals) restraint stress. In CIE rats, the ACTH response to the 3$^{rd}$ stress was blunted, and the CORT response to the 3$^{rd}$ stress recovered faster to baseline compared to the 1$^{st}$ stress. Stress-induced increases in self-grooming behavior, an adaptive response involving CRF-expressing PNCs that reflects the process of restoring behavioral homeostasis disturbed by stressors, were impaired in CIE rats. These data implicate altered CRF and NMDAR signaling mechanisms in CIE-induced maladaptive HPA axis behavioral and hormonal responses to repeated stress.

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**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH R01 AA021275

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**Title:** Functional neurocircuitry of vasopressin-mediated alcohol withdrawal-induced anxiety

**Authors: *R. K. BUTLER**[1], D. J. KNAPP[2], H. E. CRISWELL[2], G. D. STUBER[3], G. R. BREESE[4]
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**Abstract:** Chronic ethanol exposure induces neurobehavioral maladaptations in the brain, yet the precise characteristics of these changes have not been fully explored. The vasopressin receptor system in the central amygdala (CEA) regulates anxiety-like behavior ("anxiety") and may regulate alcohol effects. We explored whether adaptations occur due to chronic ethanol exposure in the CEA vasopressin receptor system or the afferent functional amygdala neurocircuitry which leads to anxiety in rats. Previously it has been demonstrated that 15 days of continuous 4.5% ethanol exposure or chronic intermittent ethanol (CIE) exposure comprised of three cycles of 4.5% ethanol for 5 days followed by 2 days of withdrawal induce social interaction deficits (elevated anxiety) in adult Wistar rats, effects we confirm in this study. Chemogenetic deactivation of projection neurons (previously determined to be $Ca^{2+}$/calmodulin-dependent protein kinase II-positive) in the basolateral amygdala (BLA) reduced anxiety following 15 days of continuous ethanol exposure. Vasopressin microinjected into the bilateral CEA (4 nmol in 0.5 µL ACSF per side) in lieu of the first two cycles of ethanol with CIE was sufficient to induce anxiety. Microinjection of a vasopressin receptor antagonist into the bilateral CEA (SSR149415; 5µg in 0.5 µL ACSF per side) at the start of the first two withdrawal cycles suppressed anxiety in this model. Preliminary data suggest that chemogenetic activation of projection neurons of the BLA in lieu of the first two cycles of CIE are sufficient to induce anxiety–an effect not observed with vasopressin receptor antagonism. Slice electrophysiology suggests that there are adaptations to the release of vasopressin and not vasopressin receptor function in the CEA as a result of CIE. Taken together, this study demonstrates a role of CEA vasopressin and the BLA to CEA circuit in the development of anxiety induced by chronic ethanol withdrawal. Such information is valuable for elucidating the co-morbidity of anxiety and alcohol withdrawal and for identifying novel therapeutic targets for associated disorders.

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**Poster**

**517. Comorbidity and Risk Factors for Alcohol Use Disorder**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Effect of chronic alcohol use on total plasma proteins, albumin and globulins levels among HIV-infected patients on d4T/3TC/NVP treatment regimen during the 9 months follow up period

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**Abstract:** Chronic ethanol use in alcoholic beverages including beers, wines, spirits, liquors and traditional brew remain a global challenge including among HIV-infected patients on treatment regimens. Study determined effect of chronic alcohol intake on total plasma proteins, total globulins and albumin among HIV-infected patients on d4T/3TC/NVP treatment regimen in Uganda. A case control study using repeated measure design with serial measurements model was used. WHO alcohol use disorders identification test (AUDIT) tool and chronic alcohol use biomarkers were used to recruit study participants. Study was approved by relevant IRB and Helsinki declaration on use of human subject in research was followed. Alcohol use biomarkers standardized gender differences in alcohol use. Total of 41 patients (21 alcohol and 20 control group) were followed up for 9 months with blood sampling at 0, 3, 6 and 9moths. Plasma proteins levels were determined by Cobas Integra 400 Plus analyzer system. Mean total plasma proteins levels in biomarkers group were higher in alcohol group during 9 month follow up with highest levels (83.12±12.41g/l) observed in $9^{th}$ month and were above normal reference ranges (64.0-83.0g/l); and were statistically significant ($p \leq 0.05$) in $6^{th}$ and $9^{th}$ month. Similar trend was observed in AUDIT tool group, were within normal reference range though statistically insignificant ($p \geq 0.05$). Mean plasma albumin levels in both AUDIT and biomarkers groups were higher in alcohol group and were statistically significant ($p \leq 0.05$) for biomarker group during entire follow up period. Similar trends was also observed in mean total globulins levels and were above normal reference range (25.0-35.0g/l) in $3^{rd}$, $6^{th}$ and $9^{th}$ of follow up and were statistically significant in $6^{th}$ and $9^{th}$ month of follow up in biomarker group. Chronic alcohol use by HIV-infected patients on d4T/3TC/NVP treatment regimen affected the total plasma proteins, total globulins and albumin levels in HIV-infected patients.

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**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Grant-in-Aid for Research Activity start-up 16H07463

**Title:** Sex differences in drinking behavior following stress in mu-opioid receptor knockout mice

**Authors: *Y. MORIYA**[1,3], Y. KASAHARA[4,3], F. S. HALL[5], Y. HAGINO[2], G. R. UHL[6], K. IKEDA[1], I. SORA[7,3]
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**Abstract:** OBJECTIVE: Adverse life experiences are associated with an increased risk of developing alcohol use disorders (AUD). Female drinking levels and drinking problems are increasing and more closely approximating those seen among men. One factor that has not been adequately examined in previous studies of the genetic contributions to AUD is sex, which is a substantial shortcoming in the field given that there are significant influences of sex on alcohol consumption patterns and alcoholism in humans and in animal models. Genetic factors, such as allelic variation in opioid receptor system genes, have a substantial influence on alcohol consumption, but only a limited set of such genetic influences on behavioral activity associated with forced drinking have been examined. In our previous study, disturbances of mu-opioid receptors influenced the effects of isolation-rearing on ethanol consumption in a sex-dependent manner. The preset study was based on the hypothesis that the effects of restrain stress on ethanol consumption, would be also influenced by both sex and the functioning of mu-opioid receptor systems. METHODS: The effects of restrain stress on ethanol intake were assessed using a two-bottle home-cage consumption (8% v/v ethanol vs. water) paradigm in male and female wild-type and mu-opioid gene knockout mice. Body weight and food, ethanol, and water consumption were measured daily. Furthermore, male and female wild-type and mu-opioid receptor gene knockout mice were studied during forced ethanol drinking, continuous access to ethanol (8% v/v) for twelve days, after which all mice were tested for locomotor activity in an open field apparatus. RESULTS: Restraint stress modestly increased ethanol consumption in female mu-opioid knockout mice but not in female and male wild-type mice. Ethanol consumption was stable in the non-stress group over the 14-day period of observation. In female mu-opioid mice, ethanol intake was greater during the stress period compared to the non-stress

mu-opioid knockout mice. On the beginning day in the first two-bottle test, food intake and water consumption were significantly reduced in all mice. The locomotor activity with forced alcohol drinking among male and female wild-type and mu-opioid knockout mice were not significantly different. CONCLUSIONS: The study shows that disturbances of mu-opioid receptors influences the behavioral consequences of ethanol consumption following stress in a sex-dependent manner.

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**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

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**Program#/Poster#:** 518.02/SS60

**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** Sex differences in alcohol consumption, object recognition and rearing in male and female high alcohol drinking (had-1) rats

**Authors: *N. MITTAL**[1], A. MARTINEZ[2], S. M. FLEMING[4], W. MADDOX[5], T. SCHALLERT[3], C. L. DUVAUCHELLE[6]
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**Abstract:** Excessive alcohol consumption has a negative impact on social and emotional well-being and the ability to think and reason. Rodent models such as selectively bred high alcohol-consuming rat lines, such as the “HAD-1” lines have been successful in furthering our understanding of the biological underpinnings that drive alcohol consumption. The present work examined sex differences in alcohol consumption, object recognition and rearing in male and female HAD-1 rats. Naïve male and female HAD-1 rats were tested in an object recognition test (ORT), followed by 4 wks of 24-hr alcohol consumption sessions. The ORT was performed in two phases, a Training Phase and a Testing Phase. For the Training Phase, each rat was placed in an open field for 600 seconds. The floor of the arena was divided into four sections labeled A-D and two identical objects were placed in Section A. Rats were videotaped while exploring the open field for 10 minutes. The rat was then removed, placed back in the homecage for one hour

and then entered the Test Phase. Here, all procedures were identical except that one of the objects was replaced with a novel object. Time in each section, time in contact with each object, and number of rears were recorded for training and testing phases. One week later, animals were given 24-hour 3-bottle access (water, 15% EtOH, 30% EtOH) every other day for 4 wks. Results: during Training, female HAD-1 rats spent significantly more time in Section A with the objects than male HAD-1 rats [$t(14)=4.51$, $p<0.001$], they actively investigated the objects more [$t(14)= 3.91$, $p<0.002$] and made significantly more rears than males [$t(14)=4.18$, $p<0.001$]. During Test, females showed a marginally significant increase in time spent in Section A compared to males [$t(14) = 2.063$, $p=.058$], but object investigation time and number of rears did not statistically differ between females and males. Female HAD-1 rats also consumed significantly more alcohol than their male counterparts [$t(14) = 2.770$, $p<0.02$]. Moreover, across all animals there was a significant correlation between exploratory behavior and alcohol consumption levels. These results indicate significant sex differences in cognitive and/or emotional reactivity and alcohol consumption female and male HAD-1 rats.

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**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

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**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** Late-aging alters behavioral sensitivity to ethanol in a sex specific manner in Fischer 344 rats

**Authors: A. E. PERKINS**[1], A. S. VORE[1], E. I. VARLINSKAYA[2], *T. DEAK[3]
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**Abstract:** Early developmental differences in numerous ethanol (EtOH)-related effects are now well established, with adolescents showing reduced sensitivity to the sedative effects of ethanol, whereas they exhibit enhanced sensitivity to the social facilitating aspects of EtOH. However, late aging-related differences in sensitivity to ethanol have been largely unexplored. Furthermore, whether aged males and females differ in the response to EtOH is unknown. Thus, two experiments were conducted to examine the behavioral responses to EtOH across a range of

doses in adult (3-month) and aged (18-month) male and female Fischer (F) 344 rats. First, a within-subjects design was used to assess social behavior in response to Vehicle, 0.5 g/kg ethanol, and 0.75 g/kg EtOH, with a day off between tests. Rats were injected (i.p.) and immediately placed into a testing apparatus for 30 min, after which a novel sex-matched adult conspecific was introduced for a 10 min social interaction test. Social investigation and contact were lower in aged animals overall and higher in females, relative to males. Interestingly, in aged females, social contact was increased following a 0.5 g/kg EtOH injection, whereas the same dose suppressed social contact in aged males. Additionally, total social behavior (investigation + contact) was decreased in both males and females following a 0.75 g/kg EtOH injection. After a 1-2-week washout period, the same rats were used to assess aging-related differences in behavioral sensitivity to the sedative effects of EtOH using Loss of Righting Reflex (LORR). All rats were administered 3.5 g/kg EtOH, i.p. Latency to lose the righting reflex and sleep time were measured. Although latency to lose the righting reflex did not differ as a function of age or sex, aged rats took substantially longer to awake relative to young adult animals. This was accompanied by significantly lower BECs at awakening, indicating increased sensitivity to the sedative effects of ethanol. In addition, females recovered faster than males and had lower BECs at awakening, consistent with reduced sensitivity to ethanol. Taken together, late aging is associated with altered sensitivity to the social facilitating effects and sedative effects of ethanol. Future studies will explore the role of aging-related inflammation in mediating the behavioral response to ethanol in late aging.

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**Program#/Poster#:** 518.04/SS62

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIMH Grant MH087583

NIMH Grant MH099085

**Title:** Alcohol intake affects ketamine self-administration in a sex-dependent manner

**Authors: *C. E. STRONG**, K. N. WRIGHT, M. KABBAJ
Biomed. Sci., Florida State Univ., Tallahassee, FL

**Abstract: Abstract:** In clinical settings**,** ketamine provides rapid and sustained antidepressant relief in patients considered to have treatment-resistant depression (TRD). More recently, ketamine has also shown promise in reducing drug craving in people suffering from substance

use disorders (SUD). Additionally, both preclinical and clinical studies demonstrated a clear interaction between ketamine and alcohol, two drugs that are recreationally abused. It is therefore critical to investigate the potential interaction of ketamine and alcohol and the potential mechanisms of this interaction. In the present study, we used the intermittent alcohol 2-bottle choice (IA2BC) paradigm and ketamine self-administration (0.5 mg/kg/infusion) to examine interaction between alcohol and ketamine. Male and female Sprague-Dawley rats were maintained on the IA2BC paradigm for ten week, with ketamine self-administration nested from week four to seven. The final three weeks of the IA2BC paradigm were used to examine the effects of alcohol on the incubation of ketamine craving. Our preliminary results indicate that alcohol affects ketamine self-administration in a sex-dependent manner, however both sexes displayed enhanced drug craving. Further work will investigate nucleus accumbens (NAc) protein expression of plasticity biomarkers such as AMPA-receptor 1 (GluA1) and postsynaptic density protein 95 (PSD95) expression as well as dendritic spine density of NAc medium spiny neurons. Together, our work will provide some insight on the mechanisms mediating interaction between alcohol and ketamine in both male and female rats.

**Disclosures: C.E. Strong:** None. **K.N. Wright:** None. **M. Kabbaj:** None.

**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 518.05/SS63

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Miami University Department of Psychology

Miami University College of Arts and Sciences

**Title:** Investigating sex differences in striatal control of aversion-resistant alcohol-drinking in mice

**Authors: *A. K. RADKE**, B. DAMES, J. FRANKEL, A. NADER, O. RAMSEY, D. SCHLEICHER, J. SETTERS, R. D. WHITE
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**Abstract:** One characteristic of alcohol use disorder is persistent seeking and taking of alcohol despite negative consequences. This “compulsive-like,” “aversion-resistant,” or “inflexible” drinking is often modeled in rodents by adding the bitter tastant quinine to alcohol (Lesscher and Vanderschuren 2012). While this approach is commonly employed in both rats and mice, there have been few examinations of aversion-resistant alcohol drinking in female animals. This gap in the literature persists despite the fact that both human and animals studies suggest females are

more vulnerable to addictive behaviors, including initiation, escalation, and relapse of drug-seeking (Anker and Carroll 2010). Here, we investigated aversion-resistant alcohol-drinking in male and female C57BL/6J mice. We used a version of the "drinking in the dark" procedure to model binge-like drinking (15% ethanol vs. water for 2 hours, 3 hours into start of the dark cycle) and tested for aversion-resistant drinking by adding quinine (100 or 250 µM) to the ethanol solution (EtOH+Q). We also assessed the role of the nucleus accumbens (NAc) in aversion-resistant drinking with chemogenetic inhibition. The DREADD vector AAV-hSyn-hM4D(Gi)-mCherry (ADDGENE) was expressed in the NAc and mice were tested for aversion-resistant drinking following injections of the DREADD ligand clozapine-n-oxide (CNO, 1 mg/kg i.p.) or vehicle. Our results demonstrate increased alcohol consumption and escalation of drinking in female vs. male mice. There were no sex differences in consumption of EtOH+Q. Finally, NAc inhibition increased consumption of EtOH+Q, and females were more sensitive to this effect than males. Additional experiments will assess the effects of inhibiting dorsal striatum on aversion-resistant drinking. Together, our results provide insight into the neural mechanisms of alcohol use despite negative consequences. Research supported by the Department of Psychology and College of Arts and Sciences at Miami University.

**Disclosures:** **A.K. Radke:** None. **B. Dames:** None. **J. Frankel:** None. **A. Nader:** None. **O. Ramsey:** None. **D. Schleicher:** None. **J. Setters:** None. **R.D. White:** None.

**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 518.06/SS64

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NSF CAREER IOS 1354408

**Title:** Sex differences in the effect of acute alcohol treatment on tyrosine hydroxylase immunoreactivity in the mesolimbocortical dopamine pathway in mice

**Authors: *E. RHINEHART**[1], D. E. WILSON[1], N. KOMARA[1], M. LATOURETTE[1], J. E. GRISEL[2]
[1]Dept. of Biol., Susquehanna Univ., Selinsgrove, PA; [2]Dept. of Psychology, Bucknell Univ., Lewisburg, PA

**Abstract:** There is a notable sex difference in how alcohol effects physiology and behavior. Females require less alcohol to become intoxicated and may have an enhanced susceptibility to addiction. Alcohol increases dopamine signaling in the mesolimbocortical dopamine reward pathway, but this could occur in a variety of ways, such as increased release, increased receptor density or decreased reuptake transport. In addition, alcohol stimulates GABA signaling, which

indirectly affects dopaminergic signaling in the reward pathway. Another possible way that alcohol could stimulate dopaminergic signaling in the reward pathway is by increasing in the production of tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. Therefore, we hypothesized that acute alcohol intoxication increases tyrosine hydroxylase protein expression to stimulate dopaminergic signaling in the reward pathway in a sex-dependent manner. To test this hypothesis, male (n=16) and female (n=16) wild-type Swiss Webster mice were injected intraperitoneally with 2g/kg ethanol or saline. Two hours post-injection animals were sacrificed by overdose with sodium pentobarbital and perfused with saline followed by 4% paraformaldehyde. Brains were removed and post-fixed in 4% paraformaldehyde followed by a 30% sucrose sink. 35 micron thick brain sections were processed for immunohistochemical staining for tyrosine hydroxylase (Anti-TH, 1:3000, EMD Millipore). In female mice, ethanol treatment increased tyrosine hydroxylase positive cells in the ventral tegmental area (139 $\pm$ 20 vs. 191 $\pm$ 25 cell number, $p<0.05$) and increased tyrosine hydroxylase fiber immunoreactivity in the nucleus accumbens (19 $\pm$ 9 vs. 56 $\pm$ 15, A.U., $p<0.05$). Tyrosine hydroxylase expression in the reward pathway was unaffected by ethanol treatment in males. The results of this study indicate that the reward pathways in the brain respond differently to acute ethanol intoxication in males and females, and it has further implications for understanding mechanisms underlying alcohol addiction.

**Disclosures: E. Rhinehart:** None. **D.E. Wilson:** None. **N. Komara:** None. **M. Latourette:** None. **J.E. Grisel:** None.

**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 518.07/SS65

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant R21AA023072

DEARC Pilot grant NIH P50AA01782306

**Title:** Sensitivity to ethanol-induced hypnosis varies across estrous cycle: Mediating role of progesterone, mGluR5 and $GABA_A$ receptors

**Authors: *N. CAMERON**, D. POPOOLA
Dept. of Psychology, Binghamton Univ., Binghamton, NY

**Abstract:** Sensitivity to ethanol-induced hypnosis is modulated by endogenous gonadal hormones levels and both the γ-aminobutyric acid (GABA) and glutamate systems. This study examined associations between variations in female sensitivity to ethanol-induced hypnosis,

across estrous cycle and fluctuations in gonadal hormones levels as well as GABA type-A ($GABA_A$) and metabotropic glutamate (mGlu) receptors functions.
Experiment 1a tested female rats at proestrus, estrus, metestrus or diestrus stages of the estrous cycle for sensitivity to an acute 3.5g/kg ethanol dose-induced hypnosis using the loss of righting reflex (LORR) paradigm. Experiment 1b tested sensitivity to motor impairment induced by gaboxadol, a selective $GABA_A$ δ subunit agonist, across the estrous cycle. Experiment 2 investigated the specific role of progesterone in sensitivity to ethanol-induced hypnosis, by administering 1000ug of progesterone to adult male rats, five times at 12-hour intervals and testing them for LORR. Brain and plasma were collected from experiment-naïve adult female rats to quantify plasma and cerebro-cortical progesterone levels in experiment 3a. Experiment 3b quantified cerebro-cortical $GABA_A$ α1and δ subunits and metabotropic glutamate receptor subtype 5 (mGluR5) expressions.
Experiment 1a revealed that female rats were more sensitive to ethanol-induced hypnosis at proestrus compared to all other estrus cycle stages, and at metestrus compared to estrus and diestrus. In experiment 1b, females were more resilient to gaboxadol-induced motor impairment at diestrus compared to estrus. In experiment 2, progesterone-treated males demonstrated longer LORR-duration compared to the vehicle-treated group. Experiment 3a revealed that plasma progesterone was highest at both proestrus and metestrus compared to estrus and diestrus, and cerebro-cortical progesterone was highest at metestrus compared to estrus and diestrus. Lastly, in experiment 3b, $GABA_A$ δ expression was lowest but mGluR5 was higher at proestrus compared to estrus and a trend compared to diestrus.
Sensitivity to ethanol-induced hypnosis is greater when progesterone levels are highest in both sexes. In females, plasma progesterone levels are highest at proestrus and metestrus. At proestrus in the cerebral cortex, $GABA_A$ δ and mGluR5 expressions suggest their contribution in the alcohol-induced sensitivity effect. Therefore, variations in female sensitivity to ethanol-induced hypnosis varies across the estrous cycle and may be primarily mediated by variations in progesterone and the activity of mGluR5 and $GABA_A$ receptors in the cerebral cortex.

**Disclosures:** **N. Cameron:** None. **D. Popoola:** None.

**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 518.08/SS66

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Influences of experimental conditions and stress on the escalation of ethanol consumption in male and female mice

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**Abstract:** Background: Escalation of ethanol intake is an important criterion for the diagnosis of alcohol dependence. Previous conditions have produced doubling of ethanol intake over 2 weeks. However, to produce escalation that models alcohol dependence in humans, an examination of the conditions that produce maximum escalation of ethanol intake in mice was needed. Previous studies have also shown that the dopamine transporter (DAT) may play a critical role in ethanol consumption (Hall, 2003) including escalation (Houston-Ludlam and Hall, unpublished findings). DAT expression is also altered by chronic mild stress (CMS), which increases ethanol consumption in heterozygous (HET) dopamine receptor D2 knockout (KO) mice (Deli, 2015). Therefore, the effects of CMS on ethanol consumption were also examined in HET DAT KO mice. Methods: Experiments 1-3 uses adult male and female C57BL/6J mice (N=10/group) while Experiment 4 used adult male and female wild-type (WT) and HET DAT KO mice (HET) (N=5/group). Experiment 1 examined the effect of different EtOH concentrations (4%, 8%, 16% and 32% v/v) using two-bottle, 24-hr access, 2 days/wk. Experiment 2 examined different intervals of availability of 16% EtOH (1, 2, or 3 days of 24-hr access, or continuous access). Experiment 3 examined the effects of a 4 bottle preference (4%, 8% and 32% EtOH v/v; and water) with 3 days of 24-hr access/wk. Experiment 4 included 4 groups: HET control (HETC), WT control (WTC), HET + CMS, and WT + CMS. Escalation was assessed using the optimal procedure defined in Expts 1 and 2. Stressors included the following schedule each week for four weeks: damp bedding (200 ml water; 2x 9-hr and 1x15-hr), 45º cage tilt (2x 15-hr and 1x 24-hr), food deprivation (3x 9-hr), strobe lighting (300 flashes/min; 2x15-hr), and water deprivation (2x 9-hr). Results: Escalation in a 2-bottle test (Expts. 1 and 2) was dependent on concentration, interval, and sex. In Experiment 3, greater levels of consumption were observed, > 15 g/kg in males and > 20 g/kg in females, but no escalation was observed. In experiment 4, female HETC produced the greatest escalation, an effect dampened by CMS. Discussion: Both interval and concentration in a limited access procedure affected escalation of ethanol consumption over time. A 4-bottle procedure did not produce escalation of ethanol intake, but did produce very high levels of ethanol intake. The ideal conditions for escalation of ethanol intake appear to be 16% ethanol 3 days/week in C57BL/6J mice. HET DAT KO was found to affect ethanol escalation after CMS in female mice only. Further experiments are needed in order to clarify the role of DAT in stress-induced alcohol consumption and escalation.

**Disclosures: D. Muskiewicz:** None. **N. Frommann:** None. **B. Patel:** None. **A. Simon:** None. **F.S. Hall:** None.

**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 518.09/TT1

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant AA020610-04

**Title:** Gender differences in binge-like ethanol drinking and dendritic spines in the nucleus accumbens of adolescent C57BL/6 mice

**Authors: *R. I. MELENDEZ**
Dept. Anat. and Neurobio., Univ. of Puerto Rico, Med. Sci. Campus, San Juan, PR

**Abstract:** Despite the progress in delineating major aspects of adolescent brain development (e.g., enhanced synaptic glutamate plasticity and vulnerability to ethanol abuse), there are no studies addressing the impact of gender as it related to excessive ethanol drinking behavior. As such, the present study examined the impact of adolescent ethanol drinking on dendritic spine density in the nucleus accumbens of male and female C57BL/6 mice. Notably, dendritic spines are postsynaptic specializations that regulate the strength of synaptic glutamate transmission and plasticity, which is heightened during adolescent brain development. Initially, adolescent mice (P30 at start) were given every-other-day (EOD) access to 15% ethanol and water (two-bottle choice) for 2 weeks (i.e., 7 drinking sessions total); ethanol-naïve mice served as aged-matched drinking controls (n=13/group/gender). One day (24 h) after the final ethanol drinking session, mice were euthanized, the brains removed and prepared for Di-I labeling of dendritic spines in the accumbens core (n=3/group/gender). Imaris 3D imaging software was used to quantify the total number of spines and spine-class density between mushroom (‘mature’) and long-thin (‘immature’) spines. Intermittent EOD access to ethanol resulted in significant escalation (binge-like) ethanol intake in both male and female mice during the early (1-4) and late (5-7) sessions of ethanol exposure. However, the rate of escalation (slope) and propensity for consumption (intake) was significantly greater in females relative to males. The mean ethanol intake values following EOD sessions 5-7 were (in g/kg) 15.7 $\pm$ 0.9 for females and 12.9 $\pm$ 0.7 for males ($p < 0.05$). In ethanol-naïve mice, we showed no gender differences in the total number (density) of spines. However, a gender x spine class interaction was observed with females showing greater mushroom spines, compared to elevated thin spines in males. Also, the head and neck size of thin spines were significantly greater in females relative to males. Following EOD drinking, the analysis revealed a significant increase in total spine density in both males and females. Interestingly, however, the class of spines up regulated by EOD drinking also depended on gender, such that females showed elevated thin spines compared to elevated mushroom spines in males. Together, these findings indicate unique gender differences in the expression of both

ethanol escalation and dendritic spine density and morphology during adolescence. Future studies are aimed at determining the potential glutamatergic receptors and signaling proteins involved.

**Disclosures: R.I. Melendez:** None.

**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 518.10/TT2

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant AA021262

**Title:** Sex differences in ethanol consumption for alcohol preferring rats

**Authors: P. J. DARIUS**, *M. C. GONDRE-LEWIS
Anat., Howard Univ. Col. of Med., Washington, DC

**Abstract:** Excessive alcohol drinking is a nationwide problem, which has not been extensively and specifically investigated in women. Epidemiological studies suggest that among the heaviest drinkers, women experience a greater number of problems as a result of their drinking than men do. The NIAAA published that female alcoholics have death rates 50 to 100 percent higher than those of male alcoholics, including deaths from suicides, alcohol-related accidents, heart disease, stroke, and liver cirrhosis. In the current study, we focus on quantifying sex differences in alcohol drinking behavior using an operant self-administration model in rodents. Genetically alcohol-preferring (P) and non-preferring (NP) rats 3-5 months old were trained in an operant drinking chamber to lever press for a 10% ethanol reward. Ethanol delivery was set to an FR4 schedule; i.e., the rats must press the lever 4 times to receive 2 sec of access to an ethanol drinking cup. Rats were placed in the operant drinking chamber for three thirty minute sessions with two forty-five minute break periods. The number of lever presses and volume consumed were recorded as a reflection of the motivation to seek and consume ethanol. Our results showed that over a three week period, females typically lever pressed ~30% less and consumed ~17% less volume than males. When males lever pressed more robustly than females, they regularly exhibited less operant efficiency meaning that for every mL of ethanol consumed, the operant registered a greater percentage of lever presses by males than females. Interestingly, our results also revealed that while male rats usually consume more absolute volume of ethanol, female rats consistently drink ~36% more ethanol per kg of bodyweight than males do. These results suggest that while male rats are likely to work harder to consume slightly more ethanol, females are still more prone to consume significantly more ethanol than males given their size. These data provide an innate biological basis for studies on sex differences in functional brain mechanisms

following excessive alcohol consumption. It is likely that female circuitry is differentially activated in the presence of alcohol.

**Disclosures: P.J. Darius:** None. **M.C. Gondre-Lewis:** None.

**Poster**

**518. Sexual Dimorphism and Reproductive-Cycle Effects on Alcohol Use**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 518.11/TT3

**Topic:** G.08. Drugs of Abuse and Addiction

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NIH R21AA023072 to N.M.C.

**Title:** Alcohol specific effects of progesterone cycling on the amplitude of the P300 ERP component in adolescent human females

**Authors: *A. DOMINGO**, N. M. CAMERON, S. LASZLO
Dept. of Psychology, Binghamton Univ., Vestal, NY

**Abstract:** Prior research has demonstrated that the amplitude of the P300 component of the Event-Related Potential (ERP) is reduced in adolescents who are at risk for developing substance use disorders. This effect, the P3AR (P300 Amplitude Reduction), is longitudinally predictive of the development of substance use disorders in adolescents. Here, we investigated whether the relationship between the P300 and alcohol responsivity, in particular, might be modulated by progesterone cycling in adolescent females. The luteal (high progesterone) phase of the menstrual cycle has previously been shown to be associated with greater alcohol consumption. We therefore hypothesized that the P3AR, as a potential predictor of substance abuse, might be larger during the luteal phase. To examine this hypothesis, we collected ERPs from 28 adolescent females (mean age=16.3 years ± 2.5 years) while they performed two oddball P300 tasks: one to detect rare alcohol images in a stream of images of non-alcoholic drinks, and one to detect rare meat images in a stream of images of foods with no meat in them. In addition to ERPs, we collected saliva samples for subsequent progesterone assay. Participants were asked to return to the lab 2 or 6 weeks after their first visit (i.e., in the obverse of their menstrual cycle) and saliva samples and ERPs were once again collected. Results indicate that the P3AR is larger during the luteal phase of progesterone cycling, and that this is true only for alcoholic stimuli, indicating that the progesterone sensitivity of the P3AR is at least somewhat alcohol

specific. An important interpretation of this result is that if P3AR is to be used as a predictor of adolescent substance use, progesterone is a moderating factor that should be considered along with raw P3AR measures.

**Disclosures: A. Domingo:** None. **N.M. Cameron:** None. **S. Laszlo:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.01/TT4

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSERC-RGPIN 341673

**Title:** Factors influencing the acquisition and retention of spatial memories in juvenile rats

**Authors: *N. TZAKIS**, B. HOFFE, M. R. HOLAHAN
Carleton Univ., Ottawa, ON, Canada

**Abstract:** The neural mechanisms by which environmental stimuli are consolidated and stored as stable, long-lasting memory representations in the brain remain elusive. Investigations into the neural structures that mediate memory processing, and the development of connectivity patterns within those structures, have provided the foundation required to gain insight into the memory consolidation process. An understanding of how memories are stored, consolidated and used during the juvenile period, along with the variables that can influence and/or ameliorate those abilities, will provide the next step to answering the fundamental questions concerning the transference of short-term memories into remote stores. The main objective of the current work was to gain insight into the factors that can improve acquisition and retention of spatial memories. Rats were trained on the Morris water maze for 3 consecutive days and then tested either recently (24 hours after training) or remotely (3 weeks after training). The labeling of c-Fos was used as a marker for neuronal activation in the hippocampus and anterior cingulate cortex to assess the contribution of these brain regions in the expression of the recent and remote memories. P50 rats showed enhanced acquisition and recall, while P20, P22, and P24 rats showed facilitated acquisition compared to P18 rats. Rats that were mass trained showed similar acquisition to those that were space trained, however, the space training appeared to facilitate the retention of both recent and remote memories compared to the massed training. Regional analyses of c-Fos in the hippocampus and anterior cingulate will be presented. Based on the behavioral data, we conclude that we conclude that the acquisition and retention of spatial memories improves as the rat develops, and that the retention of spatial memories can be facilitated be space training.

**Disclosures:** **N. Tzakis:** None. **B. Hoffe:** None. **M.R. Holahan:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.02/TT5

**Topic:** H.01. Animal Cognition and Behavior

**Support:** OBETEEN/ANR15-CE17-0013

ORUPS/ANR16-CE37-0010

GOAL/ANR14-CE13-0014

CONACyT

**Title:** Adolescent high-fat diet intake impairs object recognition memory consolidation through hippocampal endocannabinoid system

**Authors: *G. FERREIRA**[1], Y. JANTHAKHIN[1], J. OLIVEIRA DA CRUZ[2], A. BUSQUETS-GARCIA[2], M. SANTOYO-ZEDILLO[1,3], F. NANEIX[4], J.-C. HELBLING[1], S. ALFOS[1], I. MATIAS[2], G. MARSICANO[2]
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**Abstract:** Obesity is associated with adverse cognitive outcomes. Its growing prevalence during adolescence is alarming, because this is a period of radical neurocognitive shaping. In rodent models, it was recently shown that adolescence is particularly vulnerable to the effect of high-fat diet (HFD)-induced obesity leading to impaired hippocampal-dependent memory associated with altered glucocorticoid system. However, the mechanisms underlying these cognitive deficits remain elusive. The endocannabinoid system (ECS) and type-1 cannabinoid receptors (CB1R) participate in obesity, regulate memory processes and are under the control of glucocorticoids. Thus, we assessed in mice whether the effects of adolescent HFD consumption on memory function are dependent on the ECS.
We first showed that adolescent HFD consumption impaired long-term, but not short-term, object recognition memory when mice were trained without habituation to the training context. Training induced higher 1) circulating corticosterone, 2) hippocampal endocannabinoid levels (specifically anandamide) and 3) c-Fos activation in the hippocampus, perirhinal cortex and basolateral amygdala in HFD-fed mice than in control mice. Systemic post-training blockade of glucocorticoid receptors or CB1R prevented HFD-induced memory deficits and normalized c-

Fos over-activation specifically in hippocampus. Interestingly, training-induced occlusion of in vivo hippocampal long-term potentiation was absent in HFD group but rescued after CB1R blockade. Finally, hippocampal CB1R deletion and chemogenetic inhibition of hippocampal glutamatergic cells both rescued recognition memory in HFD-fed mice suggesting that CB1R-dependent disinhibition of principal hippocampal neurons is responsible for HFD-induced memory deficits.
Together these results clearly demonstrate that HFD consumption during adolescence alters the hippocampal ECS leading to impairment of hippocampal synaptic plasticity and memory consolidation.

**Disclosures: G. Ferreira:** None. **Y. Janthakhin:** None. **J. Oliveira da Cruz:** None. **A. Busquets-Garcia:** None. **M. Santoyo-Zedillo:** None. **F. Naneix:** None. **J. Helbling:** None. **S. Alfos:** None. **I. Matias:** None. **G. Marsicano:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.03/TT6

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Fluoxetine prevents fear generalization and maintains hippocampal dependency. Implications for extinction enhancement

**Authors: *L. K. PEDRAZA CORREA**[1], R. O. SIERRA, SR[2], W. SOUZA NUNEZ[2], F. LOTZ ALVES[2], L. DE OLIVEIRA ALVARES[2]
[1]Federal Univ. of Rio Grande Do Sul, Porto Alegre, Brazil; [2]Federal Univ. of Rio Grande do Sul, Porto Alegre, Brazil

**Abstract:** The cognitive ability to generalize previous experiences allows animals to select appropriate behaviors when confronting similar situations. However, overgeneralization of fear responses to similar experiences could lead to the development of different anxiety disorders. In fact, overgeneralization has been considered an important biomarker for Posttraumatic stress disorder (PTSD). Studies in our lab have shown a relationship between memory generalization and hippocampal dependency; in that case, hippocampus is necessary for precise memory retrieval but no longer involved during retrieval of generalized memories. Nowadays, the first-line pharmacological treatment for PTSD is fluoxetine, an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Since overgeneralization is an important characteristic for the diagnosis criteria of PTSD and fluoxetine a hallmark of pharmacological treatment, here we investigated the effects of chronic administration of fluoxetine on hippocampal dependency and memory generalization and subsequent effects during fear extinction.

Rats were trained in the contextual fear conditioning (4 footshocks, 0.7mA/1s) and treated with fluoxetine (10mg/kg, I.P) during 22 days following to training. In order to evaluate memory precision, animals were tested in both the aversive and novel context after the last administration. The next day, animals underwent an extinction protocol by exposure to the training context during 30min. In order to verify the appropriate fear memory suppression, animals were tested 24h after extinction and retested 21d after extinction in order to evaluate spontaneous recovery. Additionally, chronic treatment of fluoxetine was performed only after the extinction in order to test the effects during spontaneous recovery.
Our results showed that chronic administration of fluoxetine prevents context fear generalization. This effect was strongly associated with hippocampal dependency. Interestingly, memory precision resulting from fluoxetine treatment enhances fear extinction. Despite this effect, both groups expressed spontaneous recovery, a phenomenon that can be reverted by the chronic treatment with fluoxetine between the extinction protocol and spontaneous recovery test. These results suggest that chronic treatment with
fluoxetine facilitates memory precision as well as hippocampal dependency, thus allowing the attenuation of aversive memories through fear extinction. The possibility to enhance fear extinction via preventing fear generalization or spontaneous recovery shows a dual therapeutic window to attenuate aversive fear memories.

**Disclosures: L.K. Pedraza Correa:** None. **R.O. Sierra:** None. **W. Souza Nunez:** None. **F. Lotz Alves:** None. **L. de Oliveira Alvares:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.04/TT7

**Topic:** H.01. Animal Cognition and Behavior

**Support:** ANR-16-CE37-0018-01

**Title:** Role of adult hippocampal neurogenesis in spatial memory reconsolidation

**Authors: M. LODS**[1], E. PACARY[1], W. MAZIER[1], V. CHARRIER[1], G. FERREIRA[2], F. MASSA[1], D. COTA[1], N. D. ABROUS[1], *S. TRONEL[1]
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**Abstract:** Reconsolidation is the process by which an established memory becomes stable again after being reactivated. Long-term memory stabilisation relies on structural modification and the cellular mechanisms of reconsolidation have been extensively studied. Despite the fact that new neurons are continuously added to the brain and that this adult neurogenesis play an important

role in memory processes, reconsolidation has never been addressed in the context on ongoing hippocampal neurogenesis. The goal of this study is to determine the role of adult-born neurons in memory reconsolidation. We used a behavioural protocol in the Morris water maze to demonstrate that spatial learning undergoes reconsolidation. We then found that, unlike neurons born during development, adult-born neurons that are mature or immature at the time of learning are activated by reconsolidation. In order to investigate a causal relationship between adult neurogenesis and spatial memory reconsolidation, we designed a DREADD retrovirus. When injected into the dentate gyrus of rats, this retrovirus allows us to specifically and reversibly inhibit new neurons during the reconsolidation process. Our preliminary data show that inhibiting, at the time of reactivation, mature neurons that were activated by learning, has no effect on memory retention. However, inhibiting, during reconsolidation, the population of new neurons that was immature at the time of learning and not activated by learning impairs memory retention. These results suggest that adult-born neurons may be necessary for remote memory reconsolidation. All together our results show a clear involvement of hippocampal neurogenesis in spatial memory reconsolidation.

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.05/TT8

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant R15 MH100689

**Title:** Additive effects of NMDA receptor and protein synthesis inhibition on the reconsolidation of context fear discrimination memory

**Authors: *D. E. KOCHLI**[1], T. L. CAMPBELL[1], E. W. HOLLINGSWORTH[1], R. S. LAB[1], A. F. POSTLE[2], M. M. PERRY[1], V. C. MORDZINSKI[1], J. J. QUINN[1]
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**Abstract:** Mixed evidence exists regarding the role of NMDArs in memory reconsolidation. Some evidence suggests that antagonism of NMDArs is sufficient to disrupt memory reconsolidation, while other evidence suggests that activity downstream of NMDArs is critical for the induction of memory lability. The present work addresses this question using a context fear discrimination approach in which one context (CTX+) is consistently paired with footshock

while the other (CTX-) is never reinforced. Omission of a footshock during the reactivation session constitutes a prediction error, a critical boundary condition gating the induction of reconsolidation. We show that pre-reactivation administration of the NMDAr antagonist MK-801 attenuates freezing behavior during the reactivation session. Additionally, we show that pre-reactivation systemic NMDAr antagonism, combined with post-reactivation intra-BLA protein synthesis inhibition, disrupts the reconsolidation of a context fear discrimination memory—but this pattern of results only emerges following extinction training. Further, NMDAr or protein synthesis inhibition alone produce no effect. These data suggest that NMDArs play a role in memory reconsolidation, but antagonism alone may be insufficient to disrupt reconsolidation. We posit that the deficit emerging following extinction is attributable to a behavioral ceiling induced by strong behavioral training. This deficit is only detectable after the memory is sufficiently weakened by the acquisition of a competing extinction memory. Thus, it may be worthwhile to extinguish behavior following apparently null results (a common outcome in reconsolidation research), as the deficit may be obscured.

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.06/TT9

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Involvement of hippocampal cannabinoid type-2 receptors in the reconsolidation of specific and generalized contextual fear memory

**Authors: *R. S. SILVA**, M. GIACHERO, L. J. BERTOGLIO
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**Abstract:** The endocannabinoid system plays a key neuromodulatory role during aversive memory processing. Both type 1 (CB1R) and type 2 (CB2R) cannabinoid receptors are highly expressed in many brain regions, including the dorsal hippocampus (DH), a crucial brain region for contextual fear memory reconsolidation. The central CB1 receptor has been shown to contribute on this process. Despite the presence of CB2 receptor in the DH, its role in the reconsolidation of specific or generalized fear memories remains to be understood. The aim of this study was to investigate this matter using the contextual fear conditioning. The protocol consisted of familiarization, fear conditioning (3 shocks of 1.0 mA/3s) and reactivation. One and 7 days later, animals were briefly re-exposed to the paired Context A (Tests A1 and A2). They

were also briefly exposed to a novel Context B one day after Tests A1 and A2 (Tests B1 and B2). Freezing behavior was measured as an index of fear memory. In experiment 1, rats received a bilateral infusion of vehicle (VEH) or the CB2R antagonist (AM630; 1.0 µg/side) into the DH immediately after reactivation. The AM630 treatment reduced freezing time when compared to control during both Tests A1 and A2 (Test A1: 84 ± 4% vs. 33 ± 4%; Test A2: 78 ± 3% vs. 40 ± 5%). No changes were observed during Tests B1 and B2. In experiment 2, a generalized fear memory was induced by systemic administration of yohimbine (YOH), an $\alpha_2$-adrenergic antagonist, and the effect of post-reactivation CB2R infusion into DH was assessed. Rats received a systemic administration of VEH or YOH (2.0 mg/kg) after fear conditioning, and VEH or AM630 intra-DH infusion (1.0 µg/side) or systemic administration of clonidine (CLO; 0.3 mg/kg) after the reactivation session. YOH administration potentiated the fear memory that became resistant to interference by CLO after a reactivation session. However, the post-reactivation AM630 treatment promoted fear memory reconsolidation impairment, leading to a reduction of freezing (Test A1: YOH/VEH = 91 ± 1%, YOH/AM630= 48 ± 2%; Test A2: YOH/VEH = 86 ± 2%, YOH/AM630 = 33 ± 4%). YOH also increased generalized fear response which was also attenuated by AM630 treatment after reactivation (Test B1: VEH/VEH = 17 ± 1%, YOH/VEH = 46 ± 4%, YOH/AM630 = 22 ± 3% / Test B2: VEH/VEH = 17 ± 1%, YOH/VEH = 32 ± 2%, YOH 2.0/AM630 = 10 ± 1%). Altogether, the present results highlight the contribution of DH cannabinoid type-2 receptor on reconsolidation of specific or generalized fear memory, suggesting a relevant modulatory role of CB2R in this contextual fear memory process, otherwise CB1R plays an opposite function over this process.

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.07/TT10

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Sex differences in blocking after context fear conditioning

**Authors: D. E. FELDMAN**, A. A. KEISER, *N. C. TRONSON
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**Abstract:** Previous studies from our laboratory demonstrated that females show stronger generalization after context fear conditioning, suggesting that memory retrieval is different in males compared with females. Here we aimed to determine whether the information that is retrieved in context fear conditioning differs between the sexes. Distinct brain regions mediate different aspects of fear conditioning. The hippocampus compiles distinct features of a fear-

conditioning chamber into a single context representation, the basal amygdala is critical for associations between the context representation and footshock, and the nucleus accumbens plays a role in general expressions of fear and acquisition of context fear conditioning. To examine activation of these brain regions after retrieval of context fear, we assessed cFos activation in hippocampus, basal amygdala, and nucleus accumbens after retrieval of context fear-related memory in males and females. We have previously demonstrated that males show stronger activation of dorsal hippocampus, whereas females show stronger activation in basal amygdala during retrieval of context-fear. In the nucleus accumbens, we observed strong cFos activation during retrieval in both sexes. These data demonstrate sex-specific recruitment of hippocampus and amygdala in retrieval of context fear and suggest a role for nucleus accumbens in both males and females during retrieval. To examine whether the information that is being retrieved in context fear conditioning is different between the sexes we used a blocking paradigm. Both males and females showed strong expression of context fear conditioning, however only males exhibited blocking of a subsequent tone-fear memory. These data suggest that males retrieve a context-shock association that interferes with further learning, whereas females utilize a different strategy during retrieval of context fear conditioning. Overall, our findings demonstrate unique but overlapping patterns of circuit activation between the sexes, and suggest that retrieval of context fear conditioning triggers different cognitive processes in females compared with males.

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.08/TT11

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSERC

**Title:** Context fear memory: Escaping the hippocampus

**Authors: S. KISHUN**, *H. LEHMANN
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**Abstract:** Distributed contextual fear conditioning episodes makes the memory become HPC independent, meaning increasingly reliant on non-HPC memory structures. It is unclear, however, whether distribution of the conditioning episodes alone is sufficient or whether a combination of distribution and high conditioning saliency is necessary to make the context fear memory become HPC independent. To resolve this issue, rats were trained under a distributed contextual fear conditioning protocol using either a low (0.4 mA), intermediate (0.7 mA) or high

(1.0 mA) saliency shock, after which they received either sham or neurotoxic lesions of the HPC. Approximately two weeks after the surgery, the rats were given a context fear retention test during which freezing, complete immobility except for breathing, was used an index of memory. Moreover, the study aimed to determine the brain structures supporting the HPC-independent memory by assessing post-test expression of the immediate early gene c-Fos, a commonly used marker of neural activity. During the retention test, it was found that the low saliency (0.4 mA) condition failed to induce a context fear memory. The intermediate saliency (0.7 mA) condition induced robust contextual fear conditioning, as the control rats showed high levels of freezing. The HPC-lesion group in this condition, however, showed significantly less freezing, suggesting that context fear memory, despite being acquired over repeated episodes, was HPC dependent. In the high saliency (1.0 mA) condition, both the control and HPC groups showed high and comparable levels of freezing during the test, suggesting that context fear requires “strongly salient” and distributed episodes to become HPC independent. Importantly, quantification of c-Fos expression across several structures, using unbiased stereology, revealed greater amygdala activation in the rats from the high saliency condition, including the lesion group expressing the HPC-independent context fear memory. Moreover, the c-Fos findings revealed that, regardless of saliency, the repeated conditioning increased the recruitment of the perirhinal and anterior cingulate cortices. Hence, an increased context representation in the perirhinal and anterior cingulate cortices as well as a strengthened fear representation in the amygdala can support an HPC-independent context fear memory.

**Disclosures:** **S. Kishun:** None. **H. Lehmann:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.09/TT12

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Hippocampal projections to the ventral striatum are necessary to spatial memory consolidation

**Authors: G. TORROMINO**[1], G. M. BIASINI[1], A. PIGNATARO[2], L. AUTORE[1], V. KHALIL[1], S. MIDDEI[2], A. RINALDI[1], M. AMMASSARI-TEULE[2], *A. MELE[1]
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**Abstract:** Hippocampal formation (HPC) is largely recognised as a brain structure involved in spatial memory. Recently, behavioural and molecular evidence also highlighted the importance of the ventral striatum (VS) in this process. Interestingly, the HPC and the VS are anatomically

connected through ipsilateral glutamatergic projections, arising mainly from the ventral subiculum (vSUB). The purpose of the study was to investigate the role of this pathway in memory consolidation and learning-induced plasticity. To this aim, first we retrogradely traced the vSUB/VS pathway and analysed the amount of spatial learning-induced c-fos expression within this pathway. Next, to demonstrate a causal relationship between the vSUB/VS communication and memory consolidation, we used a pharmacological disconnection approach. Mice were massed trained in the Morris water maze and immediately after training administered with the NMDA receptor inhibitor, AP-5, unilaterally in the vSUB and in the contralateral VS; control mice were injected ipsilaterally in the two brain regions. Only mice contralaterally administered in the vSUB and in the VS were impaired when tested for their ability to locate the platform in probe test 24 hrs later. These findings demonstrate for the first time a functional role of vSUB/VS pathway in spatial memory consolidation. Finally, we found that post-training administration of AP-5 in the vSUB blocks spatial learning-induced increase in dendritic spine density in the VS. Overall our findings suggest that the off-line communication between the vSUB and the VS is a necessary condition for spatial memory formation and learning induced neuronal plasticity in the VS

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

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**Program#/Poster#:** 519.10/TT13

**Topic:** H.01. Animal Cognition and Behavior

**Support:** PAPIIT IN201415

CONACyT 128259

**Title:** Inhibition of protein transcription and translation in the striatum after retrieval of inhibitory avoidance learning

**Authors: *P. BELLO-MEDINA**, A. C. MEDINA, G. L. QUIRARTE, R. A. PRADO-ALCALA
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**Abstract:** It has been found that interference with neural activity after a consolidated memory is retrieved produces an amnestic state; this has been taken has indicative of destabilization of the

memory trace that would have been produced by a putative process of reconsolidation (allowing for maintenance of the original trace). However, a growing body of evidence shows that this is not a reliable effect, and that it is dependent upon some experimental conditions, such as the age of the memory, memory reactivation procedures, the predictability of the reactivation stimulus, and strength of training. In some instances, where post-retrieval treatments induce a retention deficit (which would be suggestive of interference with reconsolidation), memory is rescued by simple passing of time or by repeated retention tests. We now report that post-training and post-retrieval inhibition of transcription and translation in dorsal striatum, a structure where both of these manipulations have not been studied, produce interference with consolidation and a transitory retention deficit, respectively. These results do not give support to the reconsolidation hypothesis and lead to the conclusion that the post-activation deficiencies are due to interference with retrieval of information. Acknowledgements: We thank Bertha Islas, Martín García, Ángel Méndez, Norma Serafín, Leonor Casanova, Nydia Hernández for excellent technical and experimental assistance. This research was supported by grants PAPIIT IN201415 y CONACyT 128259.

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

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**Program#/Poster#:** 519.11/TT14

**Topic:** H.01. Animal Cognition and Behavior

**Support:** BBSRC Grant BB/J014982/1

**Title:** Retrieval-relearning: exploiting reconsolidation to strengthen contextual fear memories

**Authors: *J. L. LEE**, L. CASSINI, C. R. FLAVELL
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**Abstract:** The reactivation of a previously-learned memory, in addition to enabling expression of that memory, can lead its destabilisation. Memory destabilization necessitates subsequent reconsolidation of the memory in order to restabilize it and integrate new information. While pharmacological disruption of the reconsolidation process results in experimental amnesia, behavioral treatment can experimentally update the memory also to diminish subsequent memory expression. However, such reconsolidation-update has thus far been explored almost exclusively in retrieval-extinction procedures. Here, we tested the hypothesis that the reconsolidation-based updating process might also be harnessed to strengthen weakly-learned

memories, using a conceptually analogous retrieval-relearning procedure. A peri-threshold level of contextual fear conditioning was employed that resulted in little subsequent contextual freezing. Brief re-exposure to the conditioned context (retrieval), followed 60 min later by a second peri-threshold conditioning session (relearning) resulted in a strong and persistent contextual fear memory. Reversal of the order of the retrieval and relearning sessions had no such memory strengthening effect. Nor was memory strengthening observed with a more extended 6-hr interval between retrieval and relearning; the latter session thereby falling outside the "reconsolidation window". The retrieval-relearning effect was critically dependent upon cellular mechanisms of hippocampal contextual fear memory destabilization. Infusion of the proteasome inhibitor clasto-lactacystin-β-lactone into the dorsal hippocampus prior to memory retrieval, but not prior to relearning, prevented the effect of retrieval-relearning to strengthen the contextual fear memory. Moreover, the retrieval session engaged cellular mechanisms of destabilization and reconsolidation, including elevated hippocampal Zif268 protein levels. Therefore, memory retrieval that leads to memory destabilization allows memories to be strengthened by subsequent additional learning. The fact that these memory gains exceed those of retrieval alone or relearning alone suggests that retrieval-relearning is a highly effective mnemonic strategy to maximise memory strengthening.

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** CAPES/Brazil

University of Birmingham/UK

FAPERJ/Brazil

BBSRC/UK

**Title:** On the transition from reconsolidation to extinction of contextual fear memories

**Authors: *L. F. CASSINI**[1], C. R. FLAVELL[1], O. B. AMARAL[2], J. L. C. LEE[1]
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**Abstract:** Retrieval of an associative memory can lead to different phenomena. Brief reactivations tend to trigger reconsolidation, whereas more extended re-exposures tend to trigger extinction. Interestingly, in both appetitive and fear cued pavlovian memories, an intermediate "null point" period has been observed, where neither process seems to be engaged. Here we investigated whether this phenomenon extends to contextual fear memory. Adult male rats (lister-hooded) were subjected to a contextual fear conditioning (CFC) paradigm, consisting of training on day 1, reactivation on day 3 and test on day 4. The duration of the reactivation session varied across experiments, lasting for 3, 5, 10, 20 or 30 min. Immediately after reactivation, the amnestic agent MK-801 was injected intraperitoneally (0.1 mg/kg). The aversive response (freezing) was automatically recorded during all sessions and used as index for memory expression. We observed that MK-801 had a significant effect with the 3-min and 30-min reactivation sessions, impairing reconsolidation and extinction, respectively. However, it did not have any significant effect with 5, 10 or 20-min sessions. To investigate if the lack of MK-801 effect was a result of late drug administration, we injected MK-801 30 min prior a 10-min reactivation session. Again, there was no observable effect of the drug, suggesting that the CFC memory is insensitive to disruption at intermediate reactivations regardless of the timing of the intervention. Finally, to determine whether the results observed here reflected a subpopulation effect rather than a genuine "null-point" (i.e. MK-801 impairing reconsolidation in some animals and extinction in others leading to no overall population effect) we performed 5- and 10-min reactivations using large cohorts of animals and correlated the freezing during reactivation and test. We expected the two parameters to correlate in controls, while such correlation would be disrupted if there were subpopulations of animals differentially affect by MK-801. These and other analyses indicated, however, that the lack of effect of MK-801 at the intermediate re-exposure durations is not likely to be a result of subpopulations effect. Rather, our results strongly indicate that in contextual fear memories there is a genuine and extended "null point" between the parameters that induce reconsolidation and extinction, in which the memory is insensitive to any effect of MK-801.

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

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**Topic:** H.01. Animal Cognition and Behavior

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**Title:** Prelimbic cortex is critical for encoding contextual fear memory storage

**Authors: S. SWARNKAR**[1], V. RIZZO[1], K. TOUZANI[1], B. L. RAVEENDRA[1], J. C. LORA[2], B. M. KADAKKUZHA[1], X.-A. LIU[1], C. ZHANG[3], D. BETEL[3], R. W. STACKMAN, JR[2], *S. V. PUTHANVEETTIL[1]
[1]Neurosci., The Scripps Res. Inst., Jupiter, FL; [2]Dept. of Psychology, Florida Atlantic Univ., Jupiter, FL; [3]Dept of Med. and Computat. Biomedicine, Weill Cornell Med. Col., New York, NY

**Abstract:** Prefrontal cortex (PFC) plays a significant role in the consolidation of long-term memories (LTM). However, the cellular and molecular mechanisms critical for memory consolidation within the medial prefrontal cortex (mPFC) microcircuit are poorly understood. Here we investigated the role of new protein synthesis in the mouse mPFC during encoding of contextual fear memory.
We assessed the changes in polyribosome-associated mRNAs in the mPFC following contextual fear conditioning (CFC) in the mouse. We performed polyribosome profiling in the mPFC to identify differentially expressed gene. The role of new protein synthesis in the mPFC was determined by focal inhibition of protein synthesis and by manipulating Homer 3, a candidate identified from polyribosome profiling in the prelimbic cortex. We identified several mRNAs that are differentially and temporally recruited to polyribosomes in the mPFC following CFC. Inhibition of protein synthesis in the prelimbic (PrL) cortex, but not in the anterior cingulate cortex (ACC) region of the mPFC immediately after CFC disrupted encoding of contextual fear memory. Intriguingly, inhibition of new protein synthesis in the PrL 6 hours after CFC did not impair encoding. Furthermore, expression of Homer 3, an mRNA enriched in polyribosomes following CFC, in the PrL constrained encoding of contextual fear memory.
In conclusion, our study identified several molecular substrates of new protein synthesis in the mPFC and established that encoding of contextual fear memories requires new protein synthesis in the PrL subregion of mPFC. This study provides direct implication of the PrL cortex in the encoding of contextual fear memories and reveals a complex temporal and spatial regulation of translation in the mPFC.

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** H.01. Animal Cognition and Behavior

**Title:** Reconsolidation of episodic memory processing

**Authors: *K. TAY**[1], J. LEE[2], M. WIMBER[2]
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**Abstract:** Memory reactivation can lead to two phenomena: memory updating/reconsolidation with possibility of having inaccurate memories and memory strengthening. In Study 1, we attempted to replicate previous findings of episodic-like memory reconsolidation that re-exposure to the initial learning context is sufficient to induce reconsolidation. In a visual list-learning paradigm, participants learned 2 lists in different ways on 2 days. The experimental group learned both lists in the same room and with the same experimenter. The control group learned the two lists in different rooms with different experimenters. At test, participants were returned to the original context and recalled images from the 1st day of learning. ANOVA unexpectedly showed no difference in intrusions of Day 2 items into Day 1 recall between Experimental and Control groups, thereby failing to replicate published findings. While the Control Group had poorer recall of Day 1 items compared to a no interference control, performance in the Experimental Group was preserved. This may reflect an effect of training context re-exposure to strengthen the memory and mitigate against the deleterious impact of interfering material. In Study 2, we tested directly the capacity of memory reactivation to facilitate memory strengthening. Participants learned visual object-scene paired associated and two days later were subjected to a retrieval test and/or further learning in the same room and with the same experimenter. When subsequently tested on the paired associate recall, participants that received retrieval followed by relearning, relearning followed by retrieval, or two relearning episodes all had greatly improved performance. Groups that received one or two retrieval episodes performed as poorly as a control group, with all three groups showing evidence of memory decay. Finally, participants that received a single relearning episode performed at an intermediate level, with mild improvement. An idea of implementing 6 hours interval in between Day 2 sessions was suggested, aimed to determine whether or not the learning effect is mediated by reconsolidation processes, showing that participants in retrieval-6 hours-relearning and relearning-6 hours-retrieval groups had improved their performance, in the same manner as retrieval-relearning and relearning-retrieval group. The common effects of retrieval-relearning, relearning-retrieval, relearning-relearning, retrieval-6 hours-relearning, relearning-6 hours-retrieval to strengthen episodic memory may reflect different underlying processes, one or more of which might be related to memory reconsolidation.

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**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** MRC Grant MR/M017753/1

**Title:** Boundary conditions on instrumental memory reconsolidation

**Authors: *C. CHENG**, J. LEE, M. EXTON-MCGUINNESS
Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom

**Abstract:** Long-term memory can integrate new information through a mechanism called reconsolidation. When reactivated, a memory can destabilize into a labile state, necessitating reconsolidation to restabilize the memory again. Instrumental memories, which associate a particular action with an outcome, have recently been shown also to undergo reconsolidation. Importantly, there appears to be a requirement for prediction error in order to destabilize the instrumental memory. Here, we studied further the behavioral regulation of instrumental memory destabilization. First, we tested the hypothesis that different memories conditioned during training compete at reactivation, thereby influencing destabilization. In particular, training could also result in context-reward learning which competes for destabilization via trace dominance. Thus, if contextual memory is weakened the instrumental memory may be easier to destabilize. Adult male rats were trained to lever press for sucrose reward for 10 days, following which memory was destabilized by shifting the reinforcement schedule to a variable-ratio (VR5). A post-training context-extinction session rendered a subsequent VR5 reactivation session sufficient to destabilize the instrumental memory, as evidenced by an amnesic effect of pre-reactivation systemic injection of MK-801. MK-801 given 6h after VR5 reactivation, or in the absence of prior context extinction, had no impact on later long-term instrumental performance. However, it may not be the context extinction session itself that is necessary, as a simple day off prior to VR5 reactivation was also sufficient to render memory labile. We hypothesized active forgetting of the contextual memory during the day off may take place. To test this we injected memantine on the day off to prevent active forgetting. Interestingly, this facilitated, rather than impaired, instrumental memory destabilization. Moreover, we tested whether the VR5 reactivation could destabilize the contextual memory, thus enabling a second reactivation to destabilize the instrumental component; however, amnestic treatment was ineffective in this, indicating the memory did not destabilize in first reactivation session. Therefore, while there are two behavioural methods, context extinction and a simple day off, which both facilitate

instrumental memory destabilisation, the mechanisms by which they do so and whether they are phenomenologically similar, remain unclear.

**Disclosures: C. Cheng:** None. **J. Lee:** None. **M. Exton-McGuinness:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** MRC, UK Grant MR/M017753/1

**Title:** Reconsolidation-disruption of instrumental lever pressing memory reduces spontaneous seeking for sucrose, cocaine and nicotine reward

**Authors: *M. T. EXTON-MCGUINNESS**, M. L. DRAME, C. R. FLAVELL, J. L. C. LEE
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**Abstract:** A key obstacle in treating addiction is the high propensity for relapse. Following advances in our understanding of memory, it has been suggested that the propensity for relapse could be reduced by weakening the maladaptive memories that support substance abuse disorders. This is made possible by disrupting the process of reconsolidation, such that an appropriately destabilised memory can be attenuated. We recently demonstrated that instrumental lever pressing memory for both sucrose and cocaine can be destabilised and reconsolidation disrupted, resulting in diminished reward seeking. Here we aimed to expand this finding, investigating whether strongly established reward memories for sucrose, cocaine and nicotine could be disrupted to reduce persistent seeking behaviour. Rats were trained to lever press for either sucrose, or an intravenous drug infusion of cocaine or nicotine; each reward delivery was paired with a short conditioned stimulus (CS) presentation. Following training rats were injected with the NMDAR antagonist MK-801 (or vehicle) 30 minutes prior to a short reactivation session, in which rats were re-exposed to the training scenario except the reward contingency was shifted; this is hypothesised to trigger a prediction error responsible for destabilising the memory trace and initiating the reconsolidation process. Rats treated with MK-801 significantly reduced their subsequent lever pressing for reward, in an extinction test the next day. Interestingly, performance was rescued by contingent presentation of the CS (a conditioned reinforcer); suggesting memory disruption was selective for the instrumental component of memory only. Our work supports not only that the mechanisms of reward-seeking are likely shared between different reinforcers, but that these reward memories can be disrupted

to reduce rates of seeking. This firmly establishes reconsolidation-disruption as a viable therapeutic avenue for reducing relapse in substance abuse disorders.

**Disclosures: M.T. Exton-Mcguinness:** None. **M.L. Drame:** None. **C.R. Flavell:** None. **J.L.C. Lee:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.17/TT20

**Topic:** H.01. Animal Cognition and Behavior

**Support:** CONACYT (237570)

PAPIIT (IN201415).

**Title:** Effects of infralimbic cortex inactivation on performance of moderate and intense inhibitory avoidance training: Anterograde amnesia, state-dependency, or both?

**Authors: *M. E. TORRES GARCÍA**, A. C. MEDINA, G. L. QUIRARTE, R. A. PRADO-ALCALÁ
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**Abstract:** We have shown that intense training protects memory from treatments that interfere with memory consolidation, administrated systemically or into specific brain regions, such as hippocampus, striatum, and amygdala. The medial prefrontal cortex (mPFC) has been proposed as a modulator of memory, particularly of aversive events. mPFC includes the anterior cingulate, prelimbic, and infralimbic (IL) cortices, and dissociable roles in memory have been described for each one of them. The aim of this work was to determine whether intense inhibitory avoidance (IA) training also has a protective effect on memory consolidation in rats treated with tetrodotoxin (TTX) in the IL. Rats were trained in IA using a foot-shock of moderate or high intensity (1.0 or 3.0 mA). TTX (3 ng/0.3 µL) or its vehicle (VEH, NaCl 0.9%/0.3 µL), was administered 25 min before training. Thirty min or 48 h later retention was measured. For a state-dependency test TTX or VEH was administered twice: 25 min before training and 25 min before the retention session. Fifteen min and 60 min after training corticosterone levels and c-Fos expression, respectively, were evaluated in rats of all groups. TTX administration impaired retention of IA trained with both moderate and high foot-shock intensities. However, this amnestic effect was state-dependent when the high foot-shock was used. In additional groups, administration of TTX immediately after training induced an amnesic effect in the 1.0 mA group,

while in the group that had been trained with 3.0 mA TTX did not produce alterations in memory consolidation. High retention scores cannot be explained by a learning impairment, as TTX-treated rats showed good retention at 30 min post-training. The corticosterone levels were significantly higher in the group that showed state-dependency. c-Fos expression was inhibited in all the TTX groups as compared with the VEH groups. These results provide evidence that IL is involved in memory consolidation only in moderate training conditions. The unexpected state-dependent effect observed after TTX infusion into IL should be looked for in other cortical areas, as, to the best of our knowledge, it has only been described as occurring in subcortical structures.
We thank Leonor Casanova, Nydia Hernández, Omar González, Ramón Martínez, Maricela Luna and Renata Ponce for technical assistance.

**Disclosures: M.E. Torres García:** None. **A.C. Medina:** None. **G.L. Quirarte:** None. **R.A. Prado-Alcalá:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.18/TT21

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Marie Curie Grant 268247

NARSAD Independent Investigator Grant 23234

Compagnia San Paolo

**Title:** Remote memories are enhanced by COMT activity trough the dysregulation of the cannabinoid system in the prefrontal cortex

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**Abstract:** The prefrontal cortex (PFC) is a crucial hub for the flexible modulation of recent memories (executive functions) as well as for the stable organization of remote memories. Dopamine in the PFC is implicated in both these processes and genetic variants affecting its neurotransmission might control the unique balance between cognitive stability and flexibility present in each person. Functional genetic variants in the catechol-O-methyltransferase (COMT) gene result in a different catabolism of dopamine in the PFC. However, despite the established role played by COMT genetic variation in executive functions, its impact on remote memory formation and recall is still poorly explored. Here we report that transgenic mice overexpressing the human COMT-*Val* gene (*COMT-Val-tg*) present exaggerated remote memories (>50 days),

while having unaltered recent memories (<24-hour). COMT selectively and reversibly modulated the recall of remote memories as silencing the COMT Val overexpression starting from 30 days after the initial aversive conditioning completely normalized remote memories. *COMT* genetic over-activity produced a selective overdrive of the endocannabinoid system within the PFC, but not in the striatum and hippocampus, which was associated with remote memories. Indeed, pharmacological blockade of CB1R on remote recall in *COMT-Val-tg* mice was sufficient to rescue memory alterations. These results demonstrate that COMT genetic variations modulate the PFC-dependent retrieval of remote memories through the dysregulation of the endocannabinoid system in the PFC.

**Disclosures: G. Contarini:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.19/TT22

**Topic:** H.01. Animal Cognition and Behavior

**Support:** PAPIIT-UNAM IN210415

PAPIIT-UNAM IN202414

CONACyT 237570

CONACyT 251634

**Title:** Intense inhibitory avoidance training prevents amnestic effect of anisomycin administration in the dorsal striatum

**Authors: *D. A. GONZALEZ FRANCO**[1], P. C. BELLO-MEDINA[2], N. SERAFÍN[3], R. A. PRADO-ALCALA[4], G. L. QUIRARTE[5]
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**Abstract:** It is well known that interference with neuronal activity in structures associated with memory consolidation after moderate inhibitory avoidance training produces an amnestic effect. However, when animals are trained under intense training conditions such interference becomes innocuous. To further analyze the protective effect of intense training against amnesic treatments, groups of Wistar rats received local administration of the protein synthesis inhibitor

anisomycin (ANI) or its vehicle (VEH) in the dorsal striatum, and then were trained in a one-trial step-through inhibitory avoidance task, using moderate or high electric foot-shock intensities (1.0 or 3.0 mA). Forty-eight hours after training retention latencies were recorded. Moreover, measurements of serotonin and acetylcholine were made in this structure. We also determined the area and intensity of inhibition of anisomycin measuring Arc (Activity-regulated cytoskeletal associated protein) protein expression in rats that received ANI or VEH. The results showed that administration of ANI produced amnesia in the group that had been trained with the moderate foot-shock intensity, but retention was not impaired when the high foot-shock intensity was used. Furthermore, the administration of ANI did not change acetylcholine content, but, in contrast, there was a significant increase in serotonin. These findings suggest that de novo protein synthesis in the dorsal striatum is not necessary for the consolidation of intense emotionally arousing experiences, and, interestingly, ANI has a differential effect on the content of acetylcholine and serotonin, both of which are involved in striatal-dependent memory consolidation of moderate inhibitory avoidance training. We thank the technical assistance of Bertha Islas, Andrea C. Medina, Nydia Hernández, Leonor Casanova, Lourdes Lara, Martín García, Sandra Hernandez and Ramón Martínez. Supported by PAPIIT-UNAM (IN210415 and IN202414) and CONACyT (237570 and 251634).

**Disclosures: D.A. Gonzalez Franco:** None. **P.C. Bello-Medina:** None. **N. Serafín:** None. **R.A. Prado-Alcala:** None. **G.L. Quirarte:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.20/TT23

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Estrogen depletion in female rats decreases glia expression in hippocampus and amygdala and affects memory formation in a “single trial learning” test

**Authors: S. ERCAN**, R. L. DAVIS, *K. S. CURTIS
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**Abstract:** Decreased estrogen has been linked with impairments in several types of hippocampal-dependent memory, including spatial working memory and object recognition, in postmenopausal women. In contrast, studies of a role for estrogen in a different aspect of memory formation - encoding, consolidation and recall - have generated controversy and conflicting findings. In animal models, open field and object recognition tests are used to assess short-term memory, or long-term memory after prolonged training. Thus, these tests have limited applicability to long-term memory which is encoded by single trial acquisition and cued-recall

and more closely mimics everyday learning experiences. The long-term synaptic plasticity that underlies many forms of memory involves not only neurons, but also astrocytes and microglia; however, it is unclear whether estrogen-induced changes in glia may be important in long-term memory associated with single trial acquisition and cued-recall. Accordingly, we evaluated these relationships in adult female rats that were ovariectomized (OVX; n = 5) or remained intact (n = 5). Rats were habituated to the test arena on Day 1-7 (10 min/day of free exploration). On Day 8, a novel object (plastic cylinder) was placed in the arena, along with the presentation of a novel odor (cinnamon) and a sound recording (146.83 Hz/10 sec duration/1 min intervals). Three days later, a 10-min recall test was conducted in the arena with only odor and sound cues present. Rats' behaviors on both days were videorecorded and evaluated offline using EthoVision software. Rats were sacrificed after the recall test; brains were removed and frozen prior to taking tissue punches from the hippocampus and amygdala to analyze markers of astrocytes (GFAP) and microglia (CD68) activation using Western blots. OVX rats oriented to and explored the location that previously contained the novel object significantly more than did intact rats during the recall test. Interestingly, after 3-4 visits to that location, the latency between subsequent visits increased more rapidly in intact rats. CD68 and GFAP expression in the hippocampus and amygdala was significantly less in OVX rats than in intact rats. These results suggest that estrogen deficiency does not impair cue-triggered, long-term memory of an object under these testing conditions, and may enhance it. Alternatively, estrogen deficiency may lead to perseveration of exploratory behaviors in response to odor and sound cues in the absence of the object. In either case, alteration of these processes occurred in parallel with changes in astrocytes and microglia expression in CNS areas classically implicated in learning and memory.

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.21/TT24

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant P20 GM109098

**Title:** Optimizing object recognition testing procedures to minimize experimental variability and maximize intra- and inter-laboratory data replicability

**Authors: *J. M. POVROZNIK**, J. W. SIMPKINS, E. B. ENGLER-CHIURAZZI
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**Abstract:** Neurological disorders are associated with substantial medical, financial, and human costs. Tools for facilitating the assessment of functional consequences of brain diseases and their therapeutic interventions are increasingly needed. One commonly utilized rodent test of episodic memory is object recognition (OR), a task with high translational validity often chosen given its ease of implementation, the short duration of testing required, and the interpretability of the simple behavioral output. This test relies on the natural proclivity of rodents to seek out and explore novelty. In brief, after an acclimatization period in an open field, animals are presented with two objects on two discrete trials. For the first trial, objects are identical. After a delay period (1-48 hours), animals are again placed in the open field and presented with two objects, one novel and one from the first trial. On these delay trials, animals with intact memory predominantly explore the new object while memory-impaired animals will not differ in their object exploration. However, inter-laboratory inconsistencies in apparatus set-up and nuances in procedural aspects of testing have led to reliability and replicability challenges within the field of pre-clinical learning and memory. To address the issues in the context of the current emphasis in reproducibility and rigor in the conduct of scientific studies, we evaluated a procedure for conducting OR that addresses two important components that often vary between laboratories that utilize this task: 1) rodent acclimatization procedures and 2) objects used during test sessions. In a series of studies, during rodent acclimatization, male mice were acclimated to both the open field apparatus, as well as a 3D-printed training object for 5-min durations for 7 consecutive days. To acclimate to the objects used during testing sessions, male mice were placed in the OR apparatus with two differently-shaped, 3D-printed objects that were both novel to the mouse for 5-min testing sessions. We sought to identify behavioral benchmarks for appropriate acclimation levels among experimental subjects prior to testing. We generally observed low levels of object exploration following this acclimation process, limiting the ability to interpret object-object differences in exploration. Importantly, this finding suggests that apparatus acclimation procedures play an important interactive role in behavior performance on OR, and provides insight into optimizing this process. It is our hope that our findings will reduce variability within an experiment and support increased replicability both within and between laboratories.

**Disclosures:** **J.M. Povroznik:** None. **J.W. Simpkins:** None. **E.B. Engler-Chiurazzi:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.22/TT25

**Topic:** H.01. Animal Cognition and Behavior

**Support:** National Institutes of Health, under Ruth L. Kirschstein National Research Service Award T32-NS058280

**Title:** Medial prefrontal cortex and secondary motor cortex are critical for the performance of an olfactory working-memory task in mice

**Authors: *A. BELLAFARD**, P. GOLSHANI
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**Abstract:** Working memory is defined by the ability to store information for short periods of time (seconds) in the absence of ongoing sensory input. While a number of brain regions vital for working memory have been identified, and persistent activity in these regions has been recorded during working memory tasks, we still do not understand the mechanisms by which an ensemble of neurons generate these ongoing activity patterns. To gain more insight into this problem, we have trained head-fixed mice to perform an olfactory working-memory task, in which head-fixed mice compare the identity of two discrete odors separated by a five second delay period. We show that mice learn the task reliably and rapidly, allowing us to assay network dynamics during both learning and performance of the task. To determine which brain regions were critical for task performance, we made stereotactic injections of muscimol into different brain regions and tested behavioral performance on the task. Muscimol injections into medial prefrontal and secondary motor cortices greatly worsened task performance, while muscimol injections into posterior parietal cortex had no effect. Using in vivo two-photon calcium imaging in mice expressing the genetically encoded calcium indicator GCAMP6s, we recorded the activity patterns of hundreds of neurons over multiple days. We find task-modulated activity in a subset of neurons during the delay period. We address the question of whether and how the ensemble of neurons can generate sequential activity, and how this activity is linked to the working-memory.

**Disclosures: A. Bellafard:** None. **P. Golshani:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.23/TT26

**Topic:** H.01. Animal Cognition and Behavior

**Support:** DGAPA-PAPIIT IN201415

CONACyT 237570

**Title:** Prefrontal cortex and memory consolidation of intense inhibitory avoidance training: Effects of anisomycin

**Authors: *A. C. MEDINA**, M. HERNANDEZ-AVILA, M. E. TORRES-GARCÍA, G. L. QUIRARTE, R. A. PRADO-ALCALÁ
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**Abstract:** The prefrontal cortex, particularly its most ventral regions, i.e., prelimbic cortex (PLCx) and infralimbic cortex, has been associated with mnemonic, emotional, and cognitive processes, as well as in the modulation of encoding of fear memory. In this work we studied the participation of PLCx in the process of memory consolidation. It has been found that with moderate intensities of an aversive reinforcer, administration of inhibitors of protein synthesis during the consolidation phase, in different structures such as the striatum and hippocampus, causes an amnestic effect; however, with higher intensities of the reinforcer memory is protected against this amnestic effect. There are no published data regarding this protective effect after interference with protein synthesis in PLCx. In the present experiment anisomycin (31.25 mg/0.5 ul) or saline (vehicle), was administered into PLCx cortex of male rats of the Wistar strain 30 minutes before training in an inhibitory avoidance task, with a moderate (1.0 mA), intermediate (2.0 mA) or intense (3.0 mA) foot-shock. Anisomycin produced an amnestic state only in the group that had been trained with 1.0 mA. Results of control manipulations demonstrated that the amnestic effect was not due to state-dependency, or to alterations in acquisition. These data indicate that the normal activity of the PLCx is essential for memory consolidation of moderate learning, but not in conditions of intense training.
We appreciate the technical assistance of Bertha Islas, Norma Serafín, Leonor Casanova, Alberto Lara, Omar González and Sandra Hernández. Work sponsored by DGAPA-PAPIIT (IN201415) and CONACyT (237570).

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**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.24/TT27

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSC 102-2410-H-006-016-MY2

MOST 104-2410-H-006-025-MY3

MOST 105-2410-H-006-019-MY2

**Title:** Effects of rottlerin and MK-801 on three stages of an aversive memory: Differential involvement of hippocampus

**Authors: *M.-H. HSIUNG**, Y.-C. CHEN, S.-J. HU
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**Abstract:** Rottlerin is a multifunctional drug that has been used to treat cancer cells in the preclinical trials. It inhibits eukaryotic elongation factor 2 kinase (eEF2K), which increases the brain-derived neurotrophic factor (BDNF) protein levels in the hippocampus. The eEF2K, which phosphorylates eukaryotic elongation factor 2 (eEF2), isone of the downstream signaling molecules of the *N*-methyl-D-aspartic acid receptor (NMDAR).Moreover, rottlerin is a mitochondrial uncoupler that affects many protein kinases, such as PKC, Akt/PKB, and extra cellular-signal-related kinases 1/2 (ERK1/2).Likewise, MK-801, a non-competitive antagonist of NMDAR, exerts a fast-acting antidepressant-like effect through the eEF2K inhibition-mediated increase of BDNF protein in the hippocampus. Both the NMDA receptor and PKC have long been implicated in the normal function of learning and memory. Blockade of NMDA receptor prevents long-term potentiation(LTP), a cellular mechanism underlying learning and memory. Furthermore, the NMDA receptors in the dorsal hippocampus are involved in the establishment of long-term memory of passive avoidance (PA) task.
PA is a one-trial learning task used to assess aversive learning and memory. It is also widely used in the preclinical research to measure avoidance/aversive behavior, which is one of the symptom clusters in the posttraumatic stress disorder (PTSD). We sought to examine the effect of two antidepressants, rottlerin and MK-801, on memory acquisition, consolidation/reconsolidation, and retrieval of the PA task. Since both rottlerin and MK-801 increase BDNF protein in the hippocampus, which plays an essential role in enhancing long-term memory, we next examined whether the effects of rottlerin and MK-801 on PA is *via* changes in BDNF and/or other biochemical mechanisms in the hippocampus.
Our results indicate that systemic rottlerin impaired memory acquisition and consolidation of PA, but had no effect on memory retrieval. Systemic MK-801 impaired acquisition of the same aversive memory, which may be confounded by drug-induced change of shock sensitivity. Intriguingly, MK-801 facilitated memory consolidation and retrievalof PA. We also found that the intra-hippocampal infusion of rottlerin significantly impaired memory acquisition and consolidation of PA, indicating the effects of rottlerin are *via* the hippocampus. However, the biochemical mechanisms in the hippocampus underlying the effects of rottlerin and MK-801 on PA memory are currently under intense investigation.

**Disclosures: M. Hsiung:** None. **Y. Chen:** None. **S. Hu:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSC 102-2410-H-006-016-MY2

MOST 104-2410-H-006-025-MY3

MOST 105-2410-H-006-019-MY2

**Title:** Sex difference in the effect of rimonabant on cocaine memory in mice

**Authors: *M.-L. LAI**, H.-A. CHANG, W. DAI, S.-J. HU
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**Abstract:** Cannabinoid $CB_1$ receptors are implicated in various forms of learning and memory, including cocaine-associated memory. Rimonabant is well recognized as a $CB_1$ receptor antagonist/inverse agonist. We previously found that systemic or intra-medial prefrontal administration of rimonabant facilitates memory consolidation of conditioned place preference (CPP) induced by a low-dose cocaine, but impairs that induced by a high dose in male wild-type mice. The current study aimed to investigate the receptor and hormone mechanisms underlying the facilitating effect of rimonabant on cocaine-induced CPP. We first examined whether $CB_1$ receptors mediates rimonabant's effect by using $CB_1$ knockout mice. We found that rimonabant neither facilitated memory consolidation of a low-dose (10 mg/kg) cocaine-induced CPP nor impaired that induced by a high dose (20 mg/kg) in male $CB_1$ knockout mice. However, it is intriguing to find that rimonabant impaired 40 mg/kg cocaine-induced CPP memory in male wild-type and $CB_1$ knockout mice, implying other receptors may be involved when cocaine dosage is high as 40 mg/kg. Moreover, rimonabant did not affect cocaine CPP memory in female wild-type and $CB_1$ knockout mice. Furthermore, the facilitating effect of rimonabant on cocaine-induced CPP was found to be mediated by increase of the plasma corticosterone levels in male wild-type mice. Next, to examine whether estrogen is involved in this sex difference effect, we examined the effects of rimonabant on a low-dose cocaine-induced CPP in vehicle-treated *vs.* estrogen-treated ovariectomized (OVX) female wild-type mice and found two interesting results. First, estrogen replacement in the OVX mice *per se* enhanced the low-dose cocaine-induced CPP memory. Second, rimonabant facilitated cocaine-induced CPP memory in the OVX mice supplied with sesame oil, while impaired the same memory in the OVX mice when combined with estrogen. Taken together, our results indicate: 1) The modulatory effect of rimonabant on cocaine-induced CPP is mediated by $CB_1$ receptors and corticosterone in male wild-type mice; 2)

Estrogen is involved in sex difference in the facilitating effect of rimonabant on cocaine-associated memory.

**Disclosures:** **M. Lai:** None. **H. Chang:** None. **W. Dai:** None. **S. Hu:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.26/TT29

**Topic:** H.01. Animal Cognition and Behavior

**Support:** MOST 105-2410-H-006-019-MY2

MOST 104-2410-H-006-025-MY3

NSC 102-2410-H-006-016-MY2

**Title:** Effects of the retrieval-extinction and extinction-retrieval procedures on cocaine-associated memory

**Authors: *Y.-C. CHEN**, H.-A. CHANG, M.-L. LAI, S.-J. HU
Psychology, Natl. Cheng Kung Univ., Tainan, Taiwan

**Abstract:** Substance abuse has been a serious health issue. Millions of people in the world are suffering adverse consequences of substance abuse. Numerous studies have tried to solve drug addiction problems by pharmacological methods. However, most of the drugs in clinical use either are less effective or cause aversive side effect. It is of importance to note that there is no pharmacological intervention available for cocaine addicts. Recently, several studies suggest that a specific behavioral procedure, a reactivation followed by an extinction, effectively attenuates drug-associated memory. Nevertheless, the underlying mechanism of this behavioral procedure is challenged under some circumstances. We therefore underwent the aforementioned behavioral procedures with some modifications on cocaine-induced conditioned place preference (CPP) paradigm in mice and examined whether the behavioral procedures are as efficient as previously described. The modifications included the reverse sequence of reactivation and extinction, the elevation of cocaine dosage, the insertion of a re-training session, and the comparison with naïve mice. Our findings indicate that there is no significant difference among the extinction only, the retrieval-extinction, and the extinction-retrieval procedures. However, we found that the effects of the behavioral procedures depend on the dosage of cocaine used in the CPP paradigm. The behavioral procedures effectively suppress the cocaine-associated memory induced by the high-dose cocaine. Furthermore, mice received all three different behavioral procedures express the same level of resistance to high-dose cocaine in the re-training and the priming sessions. On the

other hand, the behavioral procedures only attenuate the low-dose cocaine-induced CPP tested 24 h after the procedures, but not the memory tested 24 h after the re-training and immediately after the priming sessions. Therefore, the effects of the retrieval-extinction and related behavioral procedures on cocaine-associated memory reconsolidation awaits further investigation.

**Disclosures:** **Y. Chen:** None. **H. Chang:** None. **M. Lai:** None. **S. Hu:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.27/TT30

**Topic:** H.01. Animal Cognition and Behavior

**Support:** FAPEMIG Grant

AISI/FMIt estructure support

**Title:** The effects of music (Mozart's sonata) on the extinction of spatial memory

**Authors:** ***A. L. BERETA**[1], A. M. FARACO[2], J. L. D. R. LEAL[2], A. C. M. COLI[2], M. P. S. SILVA[2], C. M. F. TRESNIAK[2], P. J. O. CORTEZ[2], R. S. FARIA[2], D. A. R. MOREIRA[2]
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**Abstract:** OBJECTIVE: Investigate the impact of Mozart's music (k448) in the short and long term memories of an adult animal. METHODS : 20 young adults Wistar male rats, weighing between 120 and 180 g and 28 days old, from the laboratory of the Medical School of Itajubá,separated in two experimental groups, Mozart (n = 10) and Control (n = 10) . The Mozart group was exposed to the piano Sonata k448, for 8 hours daily, from 10 p.m. until 6 a.m. for 30 days. The Control group was exposed to ambient sound in the same period. Prior to the test, a habituation period was carried out for three days. After two days of these habituation, the rats were placed for 5 minutes in the arena to explore 2 identical objects. After 1 hour and 30 minutes of training, the animals were subjected to a Short Term Memory Test in which they explored the arena for 5 minutes in the presence of a familiar object (object A) and a new one (object B). 28 days after the Short Term Memory Test, the animals were subjected to Long Term Memory Test for 5 minutes for 5 consecutive days in which they explored a familiar object (object A) and a new object (object C). The values obtained were analyzed by Test t. Significance was defined as $p < 0.05$. RESULTS: The exploration percentage of the new object B, during the Short-term Test (2 days after the Object Recognition Training), revealed that rats of the group Mozart presented higher value (Mozart = 79.22%) when compared to the Control group (Control = 58.87%);

showing statistically significant difference (p <0.05). The exploration percentage of the new object C, during the long-term test (28 days after the Object Recognition Training), did not indicate statistically significant differences between the groups after the analysis with Test t (p> 0.05). CONCLUSION: The effect of Mozart's Sonata had significant impact on the short term memory of the rats.

**Disclosures:** **A.L. Bereta:** Other; FAPEMIG. **A.M. Faraco:** None. **J.L.D.R. Leal:** None. **A.C.M. Coli:** None. **M.P.S. Silva:** None. **C.M.F. Tresniak:** None. **P.J.O. Cortez:** None. **R.S. Faria:** Other; FAPEMIG. **D.A.R. Moreira:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.28/TT31

**Topic:** H.01. Animal Cognition and Behavior

**Support:** CNES

FRM

Région Aquitaine

**Title:** Effects of hypergravity exposure on recent and remote associative memory in rats

**Authors: J.-L. MOREL**[1], A. PULGA[1], A. VANDEN-BOSSCHE[2], *B. BONTEMPI[1]
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**Abstract:** Prolonged exposure to decreased gravity experienced by astronauts during extended spaceflights (i.e. microgravity) and its counterpart, hypergravity, which is induced at the time of lift-off and spacecraft re-entry, have been reported to alter spatial memory as measured in several ground-based rodent models of altered gravitational states. However, dissociating the effects of gravity changes on spatial memory per se from those related to alterations in spatial perceptions or locomotor activity has proven challenging. Another nongravitational factor is stress, a physiological parameter known to interfere with cognitive functions. To reduce the impact of these potential confounds, we sought to characterize the effects of hypergravity on the organization of recent and remote memory in adult Sprague Dawley rats submitted to the social transmission of food preference task (STFPT) tailored to probe nonspatial associative olfactory memory in their home cage. Chronic exposure to hypergravity at 2G was achieved by placing rats into a centrifuge. Control rats were kept in normogravity (1G). In a first protocol, hypergravity exposure lasted 60 days prior to memory testing in the STFPT. Memory retrieval

was probed either 1 day (recent) or 30 days (remote) after social interaction. Results show that control and hypergravity groups interacted similarly upon encoding. Retrieval performance was comparable, indicating that encoding, consolidation and retrieval processes were left unaffected by chronic hypergravity exposure. In a second protocol, the impact of hypergravity was restricted to the memory consolidation process. Rats were centrifuged at 2G during the 21 day post-encoding period and tested for memory retrieval at 30 days. Again, no significant difference in performance between control and hypergravity rats was observed, indicating a lack of effect of hypergravity on the formation of remote memory. Upon testing in both protocols, control and hypergravity rats exhibited comparable levels of corticosterone, ruling out any persistent effect of stress. Taken together, our results reveal no deleterious effects of hypergravity on recent and remote memory and point to mild hypergravity exposure as a potentially useful countermeasure following extended spaceflights to restore microgravity-induced physiological alterations.

**Disclosures: J. Morel:** None. **A. Pulga:** None. **A. Vanden-Bossche:** None. **B. Bontempi:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.29/TT32

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Nucleus reuniens activity during consolidation influences fear memory specificity and long-term maintenance

**Authors: *L. J. BERTOGLIO**, M. A. BICCA, F. TROYNER
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**Abstract:** The nucleus reuniens (NR) has been identified as a hub for functional connectivity between the medial prefrontal cortex and the hippocampus. Hence, one could anticipate that activity in this thalamic subregion would be decisive for processes in which both brain regions have been implicated, such as memory consolidation. The objective of the present study was to investigate whether temporary NR inactivation immediately after acquiring a contextual fear memory could interfere with its features, namely specificity and long-term maintenance. Male Wistar rats were fear conditioned to context A with three shocks and then infused intra-NR with vehicle (VEH) or the GABA-A receptor agonist muscimol (MUS). Animals were re-exposed to the paired context A (Test A) and to a novel and unpaired context B (Test B) at recent (on days 1 and 2) or remote (on days 21 and 22) time points. In both cases, MUS-treated animals presented a statistically significant increase ($p < 0.05$) in freezing time (%) during Test B when compared with VEH-treated animals ($37 \pm 3$ vs. $16 \pm 3$ and $26 \pm 4$ vs. $11 \pm 3$, respectively), indicating

impaired contextual specificity. MUS-treated animals also spent significantly more time freezing than those treated with VEH during Test A (83 ± 4% vs. 61 ± 9%) at the remote time point, which indicates increased fear memory persistence over time. When context A was paired with a single shock, behavioral pattern was consistent with that abovementioned: MUS-treated animals expressed generalized fear at both time points evaluated and higher freezing time during Test A at the remote time point. We questioned whether augmented freezing time during Test B resulted from changes in anxiety-related behaviors and/or general exploratory activity. To investigate this possibility, additional animal groups were infused with VEH or MUS into the NR immediately after contextual fear conditioning. On day 1, both groups performed Test A, and 24 h later, they were tested in the elevated plus-maze (EPM) to coincide with the temporal window used to assess freezing time during Test B. Behavioral assessment in the EPM showed no significant MUS effects on inhibitory avoidance, risk assessment or general exploratory activity, indicating the MUS-induced increase in fear expression during Test B is unrelated to altered levels of anxiety and general exploratory activity. Altogether, present results indicate that NR activity during consolidation of a fear memory modulates its specificity and long-term maintenance.

**Disclosures:** **L.J. Bertoglio:** 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.; Brazilian grant from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). **M.A. Bicca:** None. **F. Troyner:** None.

**Poster**

**519. The Hippocampal Horizon: Memory Consolidation and Reconsolidation Across Structures**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 519.30/TT33

**Topic:** H.01. Animal Cognition and Behavior

**Support:** nih

**Title:** Autophagy inhibition is required for long term depression in hippocampus

**Authors: *H. SHEN**[1], Z. LI[2]
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**Abstract:** Autophagy is a process of self-degradation that involves the formation of a membrane around a portion of the cytoplasm, sequestering proteins and organelles, and the fusion of the resultant vesicle with lysosomes for degradation. Our laboratory recently found that autophagy contributes to the turn over of synaptic vesicles. However, the significance of autophagy for postsynaptic plasticity remains unclear. Here, we show that autophagy inhibition is required for

LTD and AMPA receptor internalization in hippocampal neurons. LTD and AMPA receptor internalization are blocked by pharmacologically activating autophagy with rapamycine (RAP). In hippocampal slices from the CA1 region specific Atg5 knockout mice, in which the autophagic activity decreases in postsynaptic neurons, LTD is facilitated whereas LTP remains intact. Furthermore, contextual fear conditioning is impaired in the CA1 region specific Atg5 knockout mice. These data indicate that there is an unexpected link between autophagy and postsynaptic plasticity.

**Disclosures: H. Shen:** None. **Z. Li:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.01/TT34

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant 5RO1ARO54170-09

**Title:** Testing for cognitive impairments in a mouse model for congenital muscular dystrophy

**Authors: *A. SAYED**[1], R. B. SHER[2], G. A. COX[3]
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**Abstract: Background:** Congenital muscular dystrophies (CMDs) include over 30 types of autosomal recessive muscular disorders with an onset at birth and rapidly progressing symptoms. Clinical manifestations of CMD symptoms result in muscle weakness and resulting delayed/arrested motor abilities. Many of these disorders include respiratory, cardiac illnesses and delayed speech development.
**Our Focus:** In our project, we plan to concentrate on Congenital Muscular Dystrophy with Megaconial Myopathy (MDCMC), a rare type of CMD, in which patients manifest muscular dystrophy with enlarged mitochondria localized at the cellular periphery and severe cognitive impairments. MDCMC has been shown to arise as a result of mutation in the Choline Kinase beta (*CHKB*) gene that codes for the enzyme choline kinase beta, which helps in phosphorylating choline to phosphocholine in the Kennedy pathway in skeletal muscles. We have discovered a C57BL/6J mouse with a 1.6kb deletion in the choline kinase beta gene, which showed a phenotype as described above, making it an excellent model for the study of MDCMC. Since, then we have engineered a transgenic muscle-specific rescue mouse by injecting mouse *Chkb* gene under the control of titin promoter. Following this, and using behavioral assays and equipment, we tested for muscle strength and function in our muscle-specific rescue mice, proceeding to use them to test for cognitive impairments seen in patients.

**Results and Future Directions:** Our muscle-specific rescue mice were rescued for mitochondrial size and number as seen in our transmission electron microscopy. Muscle-specific rescues showed muscle strength and function similar to those of our controls but were not significantly different from the control mice in cognitive function. We will continue to explore cognitive function with an intensive Lipidomics analysis of tissue from brain, skeletal muscle and liver of our muscle-specific rescue and control mice using mass spectrometry. Encouraged by the success of our transgene in the rescue of MDCMC, we are now developing a gene therapy strategy with AAV vectors for direct translation in humans. Along with gene therapy we have also looked at methods of dietary modifications for the rescue and /or alleviation of MDCMC disease symptoms.

**Disclosures: A. Sayed:** None. **R.B. Sher:** None. **G.A. Cox:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.02/TT35

**Topic:** H.01. Animal Cognition and Behavior

**Support:** JSPS KAKENHI Grant (No. 25118009)

**Title:** Motion feature-based automatic identification of abnormal locomotor activity of ASD mice

**Authors: M. SHYFUL ISLAM**, S. MORIMOTO, *S. KOMAI
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**Abstract:** Behavior is an important language for social communication, which promotes mutual interactions in social context. In many neuro-developmental disorders in human, such as autism spectrum disorder (ASD), social interaction is disrupted. Appropriate diagnosis and treatment is very important for the improved quality of life of ASD patient. The diagnosis of ASD is made by its behavioral criteria, determined by a physician, which depends on her/his experience. If a physician is lack of experience, she/he may end up with a wrong diagnosis. Even in animal model of autism, classical analyses of behavior are carried out by human. Disadvantages of that are some of the important features behind the background, which are not apparently visible (subtle behavioral changes), may be overlooked, or are not analyzed due to the complexity of the behavioral connection during human performance. In addition, it is very laborious and prone to lead misinterpretation of behavioral data. To overcome laborious process, and analysis of maximum features of behavioral data (both conspicuous and subtle) for correct diagnosis of ASD, advantage of modern technology (motion feature extraction and analyzing system) can be employed. In order to preliminary screening of feasibility of employment of this system in

diagnosis of ASD, we performed computer aided motion feature extraction system for analysis of behavioral features in our present study on ASD model of mice. ASD model in mice was induced by sodium valproate. The model mice were video-recorded in an open field either in single or in paired. Then, behavioral features were extracted and analyzed. The results, obtained by using this system, clearly distinguished the subtle changes in the motion of locomotor activity of mice and even identified behavioral transition in ASD model mice from control mice. Thus, it lays the pavement for the potentiality of generalized use of this method both for animal model and for human in future.

**Disclosures: M. Shyful Islam:** None. **S. Morimoto:** None. **S. Komai:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.03/TT36

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Pilot funds from the Cancer Therapy & Research Center, UT Health San Antonio

**Title:** Vortioxetine reverses cognitive impairment induced by castration as a model of androgen deprivation therapy for prostate cancer in male rats

**Authors: *A. SHARP**[1,2], S. LERTPHINYOWONG[1,2], S. BULIN[1,2], D. PAREDES[1,2], A. SULLIVAN[2,3], I. THOMPSON[3], R. LEACH[3], J. GELFOND[3], T. JOHNSON-PAIS[3], D. MORILAK[1,2,3]
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**Abstract:** Androgen deprivation therapy (ADT) is a standard treatment for prostate cancer, but ADT induces lasting and profound cognitive impairment in a majority of patients, significantly reducing quality of life for survivors and their families. Neuroimaging studies indicate reduced grey matter volume and hypoactivity in the medial prefrontal cortex (mPFC) after ADT. Further, cognitive impairment persists and increases in severity throughout the duration of treatment, suggesting that it may be possible to slow or reverse the impairment. Vortioxetine is a novel, multi-modal antidepressant drug, which has been shown to improve cognitive impairment in depressed patients. We have shown previously that chronic vortioxetine treatment rescues deficits in reversal learning on the Attentional Set Shifting Test (AST) induced by chronic cold stress in rats. In the present study, we investigated whether ADT by physical castration in male Sprague-Dawley rats causes deficits in mPFC function, and if chronic dietary vortioxetine treatment reverses these deficits. ADT induced a deficit in cognitive set shifting on the AST, a mPFC-dependent cognitive flexibility task, and chronic treatment with vortioxetine

(28mg/kg/day) rescued this deficit (both $p<0.001$, n=6-12). We are currently investigating changes in functional plasticity in the mPFC by recording field potentials evoked by stimulating excitatory afferents from the medial dorsal thalamus. Preliminary data (n=4-6) suggest that castration induced a decrease in afferent-evoked response in the mPFC, and vortioxetine normalized the response in castrated males. We also investigated changes in gene expression in the mPFC using a microarray assay. Principle components analysis of gene expression patterns in brains from all groups confirmed a prominent effect of castration, as gene expression in the mPFC of the castrated group fed control diet was clearly distinct from the other groups. Intact rats fed both diets clustered together, and vortioxetine treatment normalized the gene expression pattern in castrated rats to an extent, bringing them closer to the intact groups. Ingenuity pathway analysis showed that genes in several pathways involved in neuronal plasticity were regulated in opposite directions by castration and vortioxetine. Experiments are underway to assess changes in dendritic morphology in mPFC after ADT and vortioxetine. These results indicate that cognitive impairment after ADT may be due to changes in plasticity-related processes in mPFC that are regulated by testosterone, and that chronic treatment with the novel antidepressant drug, vortioxetine, may be effective in reversing these deficits.

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**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.04/TT37

**Topic:** H.01. Animal Cognition and Behavior

**Support:** T32MH096678

Beatrice & Samuel A. Seaver Foundation

**Title:** Attention and its underlying neuronal circuitry in both sexes of a rat model of Fragile X syndrome

**Authors:** *C. GOLDEN[1], ***C. GOLDEN**[1], H. HARONY-NICOLAS[3], S. SONAR[2], M. BREEN[2], M. G. BAXTER[4], J. D. BUXBAUM[5]
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**Abstract: Background**: Fragile X Syndrome (FXS) is a neurodevelopmental disorder that is considered to be the most common identified monogenic cause of autism spectrum disorder (ASD) and intellectual disability (ID). FXS is caused by a reduction in the Fragile X Mental Retardation Protein (FMRP), which is encoded by the FMR1 gene. FXS patients exhibit severe deficits in attention, which is subserved by the prefrontal cortex (PFC). Additionally, prefrontal grey and white matter, as well as regional volumes, are aberrant. These abnormalities in FXS are associated with PFC-dependent cognitive impairments.
**Method**: We investigated the effects of Fmrp loss on PFC-dependent behavior and anatomy in *Fmr1* knockout (KO) rats. In order to assess attention *Fmr1* KO male and female rats were trained and tested on the five-choice serial reaction time task (5-CSRTT). In order to examine the grey and white matter integrity and volume of prefrontal regions we used magnetic resonance imaging (MRI).
**Results**: Male *Fmr1* KO rats show an increase in omissions while training on the 5-CSRTT and female *Fmr1* KO rats show an increase in omissions during baseline testing. These deficits suggest that sustained attention is impaired in *Fmr1* KO rats. Furthermore, using diffusion tensor imaging, we see increased mean and radial diffusion in the thalamus, cerebellum, hypothalamus and neocortex of *Fmr1* KO male rats compared to WT male rats. These results will be corroborated by analysis of T2 images. We will also analyze the specific PFC subregions that are known to be involved in attention, which were not independently analyzed previously.
**Conclusion**: This multi-level approach will allow for a better understanding of the neural mechanisms affected in FXS-related cognitive impairments.

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**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.05/TT38

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Methylphenidate improves different cognitive aspects in a rat model of neonatal hypoxia-ischemia

**Authors: *P. M. MIGUEL**[1], B. DENIZ[2], H. CONFORTIM[2], L. BRONAUTH[2], B. DE OLIVEIRA[2], W. DE ALMEIDA[2], P. SILVEIRA[3], L. PEREIRA[2]
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**Abstract:** The hypoxia-ischemia (HI) occurs due to complications in the perinatal period and is frequently associated with cognitive impairments. In animal models, learning and memory

deficits are well-described following neonatal HI and more recently, we have also demonstrated attentional deficits. Thereby, we recognized the face validity of the HI model to the study of attention-deficit/hyperactivity disorder (ADHD). To consider the predictive validity, it is necessary to evaluate the effects of the treatment used in the clinic for ADHD in the HI model. Thus, the aim of the study was to investigate the effect of methylphenidate (MPD) in different memory protocols and attentional flexibility in young rats submitted to neonatal HI (Ethical approve 29750). Male Wistar rats were divided into four groups (n=12-13/group): control treated with saline (CTS), CT treated with MPD (CTMPD), HIS and HIMPD. On the 7$^{th}$ postnatal day (PND), the HI procedure was performed according to the Levine-Rice protocol. From the PND 30, animals were evaluated in the novel-object recognition (NOR) task, Morris water maze (MWM) and attentional set-shifting (ASS); MPD administration (2.5mg/kg, i.p) occurred 30 minutes prior to behavioral sessions. In the NOR task, we observed a trend toward the factor lesion and treatment, indicating a lower novel-object preference index in the HIS group as well as in the MPD groups. The MPD appears to disrupt the recognition of the novel object in CT animals and did not improve the lower novel-object preference index of HI animals. In the MWM, HI groups performed poorly throughout the training compared to CT groups, being the HIMPD group similar to CT groups in days 1 and 2. In the test phase, HIS group made fewer crossings over the original platform place in relation to CTS group and the HIMPD performed similar to the other groups. In the ASS task, in Test 1, the CTMPD group had a higher number of trials and errors than CTS and HIMPD groups, demonstrating again a disruption of task performance by the MPD in control animals. In Test 2, which assess attentional flexibility, the HIS group made a larger number of trials in a longer time than all other groups, indicating that MPD administration reversed the attentional deficit of HI animals. Considering these results, we can infer that MPD clearly reverses the attentional deficit observed in HI animals but partially recovers some learning and memory parameters. Besides, the MPD treatment could, in some cases, disrupt the performance of control animals. Thus, in view of the efficacy of MPD in reversing attention and some memory deficits caused by neonatal HI, we can consider the predictive validity of the animal model of HI for the study of the ADHD.

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**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.06/TT39

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant NS086929

**Title:** Low level laser therapy improves comorbidity of posttraumatic stress disorder in rat

**Authors: Y. LI**[1], Y. DONG[1], L. YANG[1], D. TUCKER[1], *Q.-G. ZHANG[2]
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**Abstract:** Posttraumatic stress disorder (PTSD) is a pathologic response after exposure to a traumatic event. Symptoms of PTSD include intrusive memories, avoidance, negative changes in cognition, and hyperarousal. PTSD patients easily develop depressive disorders, anxiety disorders and substance use disorders, collectively named as PTSD comorbidity. The current PTSD treatment includes psychotherapy, a cognitive behavioral therapy to relieve PTSD symptoms, and pharmacological therapy, primarily antidepressants and anti-anxiety medication to relieve PTSD comorbidity. However, many patients display no beneficial effect from antidepressants and anti-anxiety medication, and the side effects are of significant concern. The aim of this study is to investigate the potential beneficial effects of Low-level laser therapy (LLLT) on comorbidity of PTSD. Three groups of Adult Sprague-Dawley rats were designated: control group, PTSD model group induced by under-water trauma (UWT), PTSD+LLLT treatment group. Immediately after model induction, PTSD+LLLT group animals were treated with LLLT for two minutes (808 nm, 25 mW/cm2, 3J/day, at cerebral cortex tissue level) which was repeated daily for 7 consecutive days. We found LLLT generates acute anti-anxiety effects with a single dose of transcranial laser treatment right after UWT. LLLT treated rats show significantly increased open arm time and entries in the elevated plus maze (EPM) test 6h post trauma. LLLT also demonstrates chronic effects after seven successive doses of laser treatment over seven days, which not only improved anxiety-like behavior in EPM, but ameliorated depression-like behavior in the force swim test. It is well established that LLLT functions via stimulating mitochondrial complex IV activity and ATP production. The potential mechanisms underlying LLLT's beneficial effects on PTSD and the connections to mitochondrial function is under investigation. In summary, our study suggests that LLLT may serve as a noninvasive and alternative medicine to alleviate the anxiety and depression comorbidity of PTSD.

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**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.07/TT40

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant AA12435

**Title:** Impaired excitatory synaptic function in medial prefrontal cortex could mediate attention deficits caused by prenatal ethanol exposure

**Authors: *R. WANG**[1,2], K. A. HAUSKNECHT[1], J. B. RICHARDS[1], S. HAJ-DAHMANE[1], R.-Y. SHEN[1]
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**Abstract:** It has been shown that prenatal ethanol exposure (PE) leads to attention deficits, but the underlying mechanisms remain unclear. Using a choice reaction time task in rats to evaluate sustained attention, we demonstrated an increase in premature response, and an increase in skewness of reaction-time distribution in PE rats. These results show PE impairs preparatory attention and increases lapse of attention.
The prelimbic (PL) area of the medial prefrontal cortex (mPFC) in rats corresponds to the dorsolateral PFC in humans, which plays a significant role in regulating sustained attention. In order to understand the potential cellular mechanisms for PE-induced impairment, we investigated the synaptic function of Layer V pyramidal neurons in the mPFC, which integrate all inputs to the mPFC and are the major output neurons of this brain area.
The results from the *in vitro* patch clamp recordings show that the excitatory synaptic strength increased in Layer V PL neurons from PE rats, compared to that from controls, illustrated by a left shift of the input-output curve. In addition, PE did not lead to changes in the probability of presynaptic glutamate release, indicated by unaltered paired pulse ratio and coefficient of variation. Taken together, these results indicate that PE enhances excitatory synaptic strength in the Layer V PL neurons by upregulating glutamate receptors. This mechanism may underlie attention impairment caused by PE.

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**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.08/TT41

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant AA022480

**Title:** Neonatal ethanol exposure produces age and sex-specific impairments in attention

**Authors: *J. A. MCGAUGHY**[1], P. A. ROBINSON-DRUMMER[2], S. MACZKO[1], D. HUTCHINS[1], M. E. STANTON[3]

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**Abstract:** Fetal alcohol spectrum disorder (FASD) is a leading cause of developmental disability and has been linked to impairments in aspects of executive function including attentional processing. In the present study, we use a rodent model of FASD to determine if this model can recapitulate the attentional deficits found in humans. Neonatal ethanol (5.25 mg/kg/day; ETOH) was administered from postnatal day (PD) 4-9 in both male and female rats. First we assessed the impact of this treatment on attentional set shifting during early adolescence. The intradimensional/extradimensional set-shifting (ID/ED) task was selected because it assesses the formation of an attentional set, the shifting of attentional set, and aspects of response inhibition. We found that the performance on all stages of the ASST was unchanged by neonatal exposure to ethanol in both male and female rats. Because our prior work has shown that neonatal exposure to alcohol confers a resistance to distraction in adult males, we aimed to replicate and extend this finding in two ways. First we assessed the effects of ETOH treatment on adult females in addition to males. Second, we tested the sensitivity of all rats to low doses of a muscarinic antagonist, scopolamine (0.0, 0.01, 0.025 and 0.05 mg/kg/mL). This drug was chosen because of the strong link to the corticopetal, cholinergic system to distractibility. As shown before by our group, ETOH males are less susceptible to distraction that sham-intubated (SI) controls after injection of vehicle. In contrast, ETOH female rats were more distractible than SI females after vehicle injection. The effects of increasing doses of scopolamine were also sex-specific. The lowest dose of scopolamine produced a stronger effect in ETOH than SI males. However, in females, there was no difference in the response to drug. Overall, these data reveal age and sex-specific effects of neonatal ethanol in a rodent model of FASD. These data suggest that differences in attentional function may reflect changes in muscarinic receptor density or function but future studies are required to better elucidate the neurochemical and neuroanatomical bases for these studies.

**Disclosures:** **J.A. McGaughy:** A. Employment/Salary (full or part-time):; University of New Hampshire. **P.A. Robinson-Drummer:** None. **S. Maczko:** None. **D. Hutchins:** None. **M.E. Stanton:** A. Employment/Salary (full or part-time):; University of Delaware.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.09/TT42

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH R01MH085666

NARSAD Independent Award 2015 to Wen-Jun Gao

**Title:** Restoring prefrontal inhibition to treat cognitive symptoms of schizophrenia

**Authors: *L. CHAMBERLIN**, B. R. FERGUSON, E. MCEACHERN, W.-J. GAO
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**Abstract:** Schizophrenia (SZ) is an intractable mental disorder, affecting patients' mood, cognition, and sensory perceptions. Antipsychotics can offer relief from hallucinations and delusions, but there is currently no effective treatment for cognitive symptoms. This is especially concerning given the significant impact of poor cognition on the severity of functional impairment. The neuropathology underlying such deficits remains poorly understood, but alterations in GABAergic interneurons are believed to play an essential role. One such alteration that has been found in both human patients and animal models is a reduction in the number of parvalbumin (PV)-expressing fast-spiking (FS) interneurons in the prefrontal cortex (PFC). These PV-FS cells are important for gamma oscillations, which in turn support working memory and cognitive flexibility, all of which are disrupted in SZ patients. To explore this in rats, we use MK801, an NMDA antagonist that reproduces many of the morphological and cognitive endophenotypes observed in SZ including a deficit in prefrontal PV neurons. We hypothesize that the loss of PV cells leads to a decrease in prefrontal GABA release, thus decreasing the power of gamma oscillations and impairing performance on a working memory task. Our preliminary data suggests that there is decreased GABAergic release in MK801-treated animals compared to controls, as measured by reductions in spontaneous inhibitory post synaptic currents (sIPSCs) in medial PFC pyramidal neurons during whole-cell recordings. Thus, we investigate here whether upregulating PV interneuron activity works as a strategy for ameliorating GABAergic deficits and cognitive impairments. We have developed a novel DREADD that expresses the excitatory $hM3D_q$ receptor under a PV promoter (PV-$hM3D_q$). We will transfect MK801-treated animals with this PV-$hM3D_q$ DREADD with the goal of normalizing GABAergic signaling in the mPFC and ameliorating cognitive deficits. This study helps to elucidate the mechanisms of cognitive dysfunction in SZ, potentially pointing the way to effective therapeutics. Future directions include *in vivo* measures of local field potentials during behavior to probe alterations in gamma oscillations associated with our MK801-treated rats and pharmacogenetic upregulation of PV interneuron activity.

**Disclosures: L. Chamberlin:** None. **B.R. Ferguson:** None. **E. McEachern:** None. **W. Gao:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.10/TT43

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Performance of heterozygous dopamine transporter mice in a 5-choice serial reaction time test for studies of attention deficit hyperactivity disorder

**Authors: *F. RESENDIZ GUTIERREZ**, D. MUSKIEWICZ, B. PATEL, A. SIMON, O. CHAKER, Y. SABER, F. S. HALL
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**Abstract: Background**: The 5-choice serial reaction time task (5-CSRTT) is used to study attention and impulsivity in mice. The test involves a specialized operant chamber in which 5 visual stimuli can be presented, which indicate which of 5 response (nose-pokes) will result in the presentation of a reinforcer. The mouse must attend to the appropriate stimulus in order to make a correct response (a measure of attention), avoid premature responses (a measure of impulsivity), or omissions (also a measure of attention). The procedure has been used to study a number of models of frontostriatal disorders in mice, including Attention Deficit Hyperactivity Disorder (ADHD). The aim of this study is to test performance in heterozygous Dopamine Transporter Knockout mice (DAT (+/-)) , a potential animal model of ADHD, with the ultimate aim of testing the effects of pharmacological treatments on attentional deficits. **Methods**: 4 Female DAT (+/-), 4 Female DAT (+/+), 4 Male DAT (+/-) and 3 Male DAT (+/+) were tested. After initial task performance is established, the subjects are tested for attentional impairments by varying the stimulus duration (SD), in order to identify conditions that are optimal (i.e. there are attentional impairments) for the testing of potential ADHD medications. Across 80 trials, stimulus duration is varied pseudo-randomly (16 trials each of 2, 1, 0.5, 0.25, 0.12, sec stimulus duration). SD is adjusted downwards so that performance is sub-optimal at the lowest durations. The goal is to establish a range of performance that degrades from optimal performance at high SD to sub-optimal performance at low and variable SD. **Results:** Female DAT (+/-) mice made more errors of omission than their (+/+) counterparts, but Male (+/-) mice made less than (+/+). There were no differences in number of premature or correct responses. **Discussion**: This paradigm will be altered in order to further assess behavioral differences between groups and be used to test the effects of both novel and putative treatments in heterozygous DAT knockout model of ADHD in both male and female subjects.

**Disclosures: F. Resendiz Gutierrez:** None. **D. Muskiewicz:** None. **B. Patel:** None. **A. Simon:** None. **O. Chaker:** None. **Y. Saber:** None. **F.S. Hall:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

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**Program#/Poster#:** 520.11/TT44

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSERC

CIHR

**Title:** A test for social behaviour in the common marmoset

**Authors: *J. CARRIOT**[1], R. J. NICOLSON[2], J. C. MARTINEZ-TRUJILLO[3]
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**Abstract:** The marmoset monkey (Callithrix jacchus) is a promising animal model for exploring social behaviors typical of humans and other primates. Here, we developed a test for assessing social preference behavior in marmoset monkeys based on pre-existing tests (e.g., the three chambers test for rodents). Two plexiglass chambers were attached to a housing cage that hosted a minimum of two animals. One of the chambers include an exercise ladder (play room) and the other chamber contained a screen showing a movie with i) peers marmosets in their natural habitat, 2) natural predators (snakes, jaguar) or 3) a pattern of squares. Animals had free access to the chambers during different experimental sessions: 1) play room vs peers, 2) play room vs predators, and 3) play room vs squares. A camera (Go-Pro Hero 4) recorded videos of the animals during several sessions that lasted a minimum of 1 hour a day. The videos were analyzed by human observers that quantified the amount of time the animals spend in each one of the chambers. Results show that during the sessions, animals spent more than 60% of the time in the experimental boxes (vs 40% of the time in the housing cage). The box showing the peers was the most interesting with a ratio of 0.79 (time in the peers box/total time in boxes during condition 1). Surprisingly, the second most interesting box was the one showing the predators with a ratio of 0.6 (vs 0.4 in the play room; condition 2). Finally, animals equally prefer the movie with the squares and the play room ($p>0.05$; condition 3). Other variables including, time of first entry, number of entries or absolute time in the chamber corroborated these results. Our results provide a relatively simple test for exploring social behavior in marmosets. They also confirm known similarities between marmosets and humans regarding their social behavior.

**Disclosures: J. Carriot:** None. **R.J. Nicolson:** None. **J.C. Martinez-Trujillo:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.12/TT45

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Edital MCT/CNPq 14/2010

Edital MCTI/CNPq 14/2013

**Title:** The SLA16 rat strain, a potential new genetic model of ADHD

**Authors: *G. S. IZIDIO**, N. GRANZOTTO, F. J. CORREA, A. P. FRANCA, P. RAMBORGER, G. FADANNI, R. B. OLIVEIRA, R. C. N. MARCHETTE
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**Abstract:** Attention Deficit and Hyperactivity Disorder (ADHD) is the most diagnosed psychiatric disorder among children and adolescents and may persist into adulthood. Currently, the animal model most widely used in preclinical studies, of this disorder, is the Spontaneously Hypertensive Rats (SHR) strain. Although very valuable, this strain has limitations, not being able to cover all the issues raised in ADHD research. Thus, we developed a congenic strain named SLA16 (SHR.LEW-*Anxrr16*). In these recombinant animals, the background genome is from SHR rats and the portion of Chromosome 4 (~86Mb or 45%) came from Lewis rats. In the present study, our main goal was compare SHR and SLA16 rat strains, in order to propose an alternative genetic model of ADHD. For this, we tested male SHR and SLA16 rats in the plus-maze discriminative avoidance task (PMDAT), open-field (OF), object recognition (OR), spontaneous alternation (SA), fear conditioning (FC) and mean arterial pressure. Moreover, we treated animals, via intraperitoneal, with caffeine (CAF) 2 mg/kg, or saline (0.9%), twice a day (12h/12h), from postnatal days 24-45, in order to evaluate locomotor activity, emotionality and working memory, at the end of treatment and a month later. For this, we used the OF and Morris water-maze (MWM) 4 trials/day, 5 days. Our results showed that SLA16 strain displayed lower levels of anxiety/emotionality and arterial pressure, higher locomotor activity and deficits in learning/memory in comparison with SHR strain. The treatment with CAF, during adolescence, appeared to decrease the locomotor hyperactivity of SLA16 and improve the working memory of SHR. Thus, we concluded that SLA16 strain represents a valuable tool in the search for genetics and neurobiological pathways of ADHD. And the treatment with CAF, during adolescence, could be an alternative way to improve endophenotypes related to ADHD.

**Disclosures: G.S. Izidio:** A. Employment/Salary (full or part-time):; UFSC. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Edital MCT/CNPq 14/2010 and Edital MCTI/CNPq 14/2013. **N. Granzotto:** A. Employment/Salary (full or part-time):; Capes. **F.J. Correa:** A. Employment/Salary (full or part-time):; CNPq. **A.P. Franca:** A. Employment/Salary (full or part-time):; CNPq. **P. Ramborger:** A. Employment/Salary (full or part-time):; Capes. **G. Fadanni:** A. Employment/Salary (full or part-time):; Capes. **R.B. Oliveira:** A. Employment/Salary (full or part-time):; Fapesc. **R.C.N. Marchette:** A. Employment/Salary (full or part-time):; CNPq.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.13/TT46

**Topic:** H.01. Animal Cognition and Behavior

**Support:** DFG Grant

**Title:** The role of brain serotonin in social and cognitive abilities : Lessons from tryptophan hydroxylase 2-deficient rats

**Authors: *L. ALONSO**[1], P. PEEVA[2], Y. WINTER[1], N. ALENINA[2], M. RIVALAN[1]
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**Abstract:** In clinical settings, selective serotonin reuptake inhibitors are often used as treatments of depression, suicide related behavior, impulse control disorder and substance use disorder. Patients with these disorders share common cognitive and social impairments such as poor decision-making abilities, risk taking tendencies, cognitive inflexibility, motor and cognitive impulsivity and higher aggression. In rats, genetic, pharmacological, and behavioral studies have suggested, testing one function at a time that a central serotonin hypofunction could lead to impairments in each of these cognitive and social functions. It is, however not yet studied how hyposerotonergia simultaneously affects the expression of these behaviors in the same animal. In humans more than one function is usually impaired in a given individual. The goal of this study was to take a more translational approach and to investigate the role of serotonin in the concomitant expression of cognitive and social abilities in rats. To model the serotonin hypofunction we used recently generated rat line lacking tryptophan hydroxylase 2 (TPH2), the rate limiting enzyme of serotonin synthesis in the brain. TPH2-deficient (*TPH2-/-*) rats are completely depleted of serotonin in the central nervous system, but have normal levels of the monoamine in the periphery. Although *TPH2-/-* rats exhibit marked growth retardation during first 5 weeks of postnatal life, the size of the animals is normalized thereafter and serotonin depletion does not affect the morphology of the adult brain. We subjected these animals to six cognitive and social tasks : the Rat Gambling Task and reversed Rat Gambling Task, the Fixed interval-Extinction schedule of reinforcement, the Delay and Probability Discounting tasks, and the Visible Burrow System. As expected Tph2-/- rats showed an increased level of aggression. Intriguingly, *TPH2-/-* rats presented unexpected high levels of cognitive abilities and they were able to establish a social hierarchy. This study is challenging the historical role attributed to serotonin and its importance for the concomitant expression of cognitive functions.

**Disclosures: L. Alonso:** None. **P. Peeva:** None. **Y. Winter:** None. **N. Alenina:** None. **M. Rivalan:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

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**Program#/Poster#:** 520.14/TT47

**Topic:** H.01. Animal Cognition and Behavior

**Support:** 7K08GM106144 - 04

**Title:** Topologically invariant manifolds of *C. elegans* pan-neuronal activity

**Authors: *C. BRENNAN**, A. PROEKT
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**Abstract:** It is still unknown to what extent brain activity is driven by stochastic versus deterministic dynamics. Studies in vertebrates exposed evidence for both types of regimes, but the sheer complexity of the vertebrate brain makes this question experimentally intractable. The expectation is that by recording the activity of all the neurons in a nervous system the true behavior of the neuronal network can be elucidated. With the advancement of neuronal imaging techniques it is now possible to create such recordings for the simplest of organisms. What type of methodologies does one use to extract the underlying forces driving the evolution of the system? Do single neurons represent one unique piece of information? Combinations of multiple neurons? Are the pan-neuronal activity of all neurons even enough to fully describe the network? Here we show that in the simple nervous system of C. elegans, we can construct single trial models that capture both the dynamic and stochastic elements of the network. However, these models fail to generalize from across multiple worms, which may seem to argue that the neuronal dynamics of each worm are unique. Using delay embedding, we discover that the long time-scale flow of neuronal activity is confined to a topologically invariant manifold. In contrast to neuronal activity, this manifold is highly conserved among individual worms. The manifold consists of two interlocked cycles of activity. While the system evolves along a cycle its behavior is well approximated by a fully deterministic model. In contrast, when the system nears the junction between two cycles, the trajectories diverge and stochastic processes dominate. We provide a method for the extraction of such topologically invariant manifolds from neuronal time series data and as a test for generality we also obtain similar results from simulated systems.

**Disclosures: C. Brennan:** None. **A. Proekt:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

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**Title:** History of winning remodels thalamo-PFC circuit to reinforce social dominance

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**Abstract:** Mental strength and history of winning play a role in the determination of social dominance. However, the neural circuits mediating these intrinsic and extrinsic factors have remained unclear. We identified a dmPFC neural subpopulation showing effort-related firing during moment-to-moment competition in the dominance tube test. Optogenetic ctivation or chemogenetic inhibition of dmPFC induces instant winning or losing respectively. Notably, *in vivo* optogenetic-based long-term potentiation or depression experiments establish that the mediodorsal thalamic (MDT) input to dmPFC mediates long-lasting changes in the social dominance status impacted by history of winning. The same neural circuit also underlies transfer of dominance between different social contests. These results reveal synaptic plasticity at the MDT-dmPFC circuit as an important neural substrate mediating both the intrinsic dominant state and extrinsic winning experience for social hierarchy determination, thereby providing a new framework for understanding the circuit basis of adaptive and pathological social behaviors.

**Disclosures: H. Zhu:** None. **T. Zhou:** None. **Z. Fan:** None. **F. Wang:** None. **Y. Chen:** None. **Z. Yang:** None. **L. Zhang:** None. **L. Lin:** None. **Y. Zhan:** None. **Z. Wang:** None. **H. Hu:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

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**Support:** NIH DA09082

NIH NRSA F31MH105211

**Title:** μ-Opioid receptor activation in the locus coeruleus increases synchronization of the male, but not female medial prefrontal cortex

**Authors: *H. M. GUAJARDO**[1], A. L. CURTIS[2], S. BHATNAGAR[3], R. J. VALENTINO[4]
[1]Neurosci. Grad. Group, Univ. of Pennsylvania, Philadelphia, PA; [2]Dept Anesthesiol., Children's Hosp. Philadelphia, Philadelphia, PA; [3]Dept Anesthesiol., Univ. Pennsylvania, Children's Hosp Philadelphia, Philadelphia, PA; [4]Div. of Neurosci. and Behavior, Natl. Inst. of Drug Abuse, Rockville, MD

**Abstract:** Stress-related neuropsychiatric pathologies are more prevalent in females compared with males. Activation of the locus coeruleus (LC)-norepinephrine (NE) system is a component of the stress response that is thought to affect cognition. Evidence suggests that endogenous opioid neuropeptides are released during stress to restrain LC activation and to facilitate a return to baseline activity when the stressor ends. Sex differences in this opioid influence could be a bases for sex differences in stress vulnerability. We previously demonstrated decreased μ-opioid receptor (MOR) mRNA and protein in the LC of female compared to male rats. As a result, LC neurons of female rats were less sensitive to inhibition by the μ-opioid receptor (MOR) agonist, DAMGO. Because the LC-NE system affects cognitive function through its projections to the medial prefrontal cortex (mPFC), the present study determined whether LC-MOR activation translates to changes in mPFC neural activity and whether there are sex differences in this effect. Local field potential (LFPs) were recorded from the mPFC of freely behaving male (n=4) and female (n=4) rats before and following local LC microinjection of DAMGO (10 pg). LFPs were analyzed as power spectral density plots and the power at different frequency bands (delta 2-4 Hz, theta 4-8 Hz, alpha 8-12 Hz, and beta 12-20 Hz) was analyzed and compared between sexes. Intra-LC DAMGO resulted in a time-dependent synchronization of mPFC activity in male but not female rats. Two-way repeated measures (rm) ANOVA with post-infusion time as the repeated measure revealed a sex X time interaction for power in delta ($F(3,6)=28.4$, $p<0.005$), a trend for sex X time interaction for power in theta ($F(3,6)=6.2$, $p=0.05$), and a sex X time interaction for power in alpha ($F(3,6)=6.9$, $p<0.05$). LC microinfusion of ACSF had no effect on mPFC activity in either male or female rats. Together, the results are consistent with previous evidence for decreased MOR function in the LC of female rats and demonstrate that this translated to a diminished effect on cortical activity. Decreased LC-MOR function in females could contribute to greater stress-induced activation of the LC and increased vulnerability of females to hyperarousal symptoms of stress-related neuropsychiatric pathologies.

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**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.17/TT50

**Topic:** H.01. Animal Cognition and Behavior

**Support:** EMBO Long-Term Fellowship

DFG SPP1665

**Title:** Impaired task-related firing and long-range 4 Hz synchrony of dopamine neurons underlies working memory deficits in a mouse model of cognitive dysfunction

**Authors: *S. DUVARCI**[1], E. H. SIMPSON[2], G. SCHNEIDER[3], E. R. KANDEL[4], J. ROEPER[5], T. SIGURDSSON[5]
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**Abstract:** The dopamine (DA) system plays a major role in cognitive functions through its interactions with several brain regions including the prefrontal cortex (PFC). Disturbances in the DA system contribute to cognitive deficits in psychiatric diseases including schizophrenia, yet exactly how they do so remains poorly understood. To address this question, we recorded single units and local field potentials (LFPs) in the ventral tegmental area (VTA) and the PFC in mice overexpressing the D2 dopamine receptor in the striatum (D2R-OE mice), a well-characterized model of dopamine-related cognitive dysfunction. Recordings were made while animals performed a non-match-to-sample spatial working memory task in a T-maze. Each trial of the task consisted of two phases. In the 'sample phase', mice ran up the center arm of the T-maze and entered one of the goal arms to collect reward, while the other arm was blocked. After a brief ~10s delay, the mice again ran up the center arm, but now both goal arms were open ('choice phase'). To obtain a reward, animals had to enter the goal arm not visited during the sample phase. As previously shown, D2R-OE mice required more training to reach criterion performance indicating a deficit in working memory (WM). To investigate the neural circuit disturbances underlying this deficit, we examined neural activity in the VTA and PFC during task performance. Specifically, we compared activity in the choice phase, where the animals had to use WM to guide their behavior, to the sample phase, where animals performed the same overt behavior but without the WM requirement. In control animals, we found that 4 Hz oscillations emerged in the PFC and VTA during the choice phase of the task. This was accompanied by increases in the phase-locking of VTA and PFC neurons to local 4 Hz oscillations. In the VTA the increase in phase-locking was specific to putative DA neurons, and was not seen in putative GABA neurons. The increase in phase-locking was observed between neurons in one structure

and 4 Hz oscillations in the other, demonstrating that 4 Hz oscillations mediate long-range synchrony between the VTA and PFC. This was further supported by a selective increase in 4 Hz LFP coherence between the two structures during the choice phase. Strikingly, we found that these WM-dependent increases in local and long-range 4 Hz VTA-PFC synchrony were absent in D2R-OE mice. Furthermore, the magnitude of this synchrony deficit correlated strongly with the behavioral deficits in the D2R-OE mice. We also found a selective disruption in the task-related firing patterns in VTA DA, but not GABA, neurons. These results identify how altered DA neuron activity contributes to cognitive impairments.

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**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.18/TT51

**Topic:** H.01. Animal Cognition and Behavior

**Support:** DFG Priority Programm SPP 1665

**Title:** Impact of task-phase specific optogenetic silencing of the medial prefrontal cortex on spatial working memory

**Authors: *P. VOGEL**, S. DUVARCI, T. SIGURDSSON
Inst. of Neurophysiol., Goethe Univ. Frankfurt, Frankfurt am Main, Germany

**Abstract:** Spatial working memory, the ability to store and update spatial information in the short term, is an essential feature of goal-directed behavior. Lesion and inactivation studies suggest that the medial prefrontal cortex (mPFC) plays a key role in the execution of spatial working memory tasks. However, little is known about the temporal structure of mPFC involvement during these tasks, that is during which phase (encoding, maintenance, and/or retrieval) it is actually engaged. In the current study we addressed this issue by recording from and optogenetically silencing mPFC neurons in a temporally specific manner while animals performed a spatial working memory task. To this end, an adeno-associated virus expressing either the neural silencer ArchT (AAV2/5-CamKII-ArchT-GFP, n=15) or eGFP (AAV2/5-CamKII-eGFP, n=6) was bilaterally injected into the mPFC of C57BL/6N mice. Two optic fibers (200 micrometer diameter) were also implanted bilaterally into the mPFC, one of which was attached to recording electrodes. Following recovery from surgery animals were trained on a non-match-to-sample spatial working memory task in a T-maze. Each trial of the task began with a “sample phase” in which mice entered one of the two goal arms to obtain a reward. After a ~10s “delay phase”, the “choice phase” began in which mice had to choose between two open

goal arms and only obtained a reward if they entered the goal arm not visited during the sample phase. Once animals had learned the task, testing sessions began in which we illuminated the mPFC with yellow light (594nm, 16mW) on half of the trials. In each testing session light delivery was temporally restricted to one of the three phases of the task (sample, delay or choice) in order to examine the contribution of the mPFC to different task components. In mice expressing ArchT light application inhibited 87% of putative pyramidal cells. Light application in ArchT animals in any of the three phases of the task also impaired spatial working memory performance while the same treatment in eGFP control animals had no significant effect on behavior. However, illuminating the mPFC in only half of the sample phase did not impair task performance. Interestingly, when the mPFC was silenced during the whole sample phase, neural activity in the following "laser-free" choice phase was increased. Our results suggest that the mPFC is involved in encoding, maintenance, and retrieval of spatial working memory content. We are currently investigating how mPFC projections to downstream structures contribute to different aspects of spatial working memory.

**Disclosures:** **P. Vogel:** None. **S. Duvarci:** None. **T. Sigurdsson:** None.

**Poster**

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ANR "GABA"

ANR IDEX PSL

ANR LABEX IEC

**Title:** Role of gamma and beta oscillatory activity sequence in a two-step working memory gating mechanism

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**Abstract:** Working memory (WM) is an ability of the brain to retain sensory information in such form that it is still available after a short time delay during which it is not directly perceived. During WM tasks, elevated neural firing rates, as well as specific modulation of oscillatory activity are observed [1,2]. During presentation of to-be-memorized stimuli, gamma oscillatory power increases and beta activity is suppressed. Subsequently beta oscillation rebounds, reaching its maximum in the middle of the delay period [2,3]. Experiments identified two cell populations ("Encode/Decode"-cells and "Maintenance"-cells), whose firing rate time-course are strikingly similar to the gamma and beta dynamics, respectively [3]. Using a computational model of working memory storage, we clarify the role of gamma and beta activity sequence in gating information to WM. Our low-dimensional model is constructed as a coupled circuit of excitatory-inhibitory neural populations: a stimulus sensitive S-population reactive to external stimuli, and a bistable "delay" D-population that incorporates short-term plasticity [4] and thus performs WM retention. The S-population exhibited gamma-band resonance, while the D-population has resonance in the beta range. Our simulations showed that stimulus-driven gamma-modulated transient input to the S-circuit provides sufficient excitation to the D-population to bring it close to the memory-retained state, while subsequent external beta-band bursts transmitted to the D-population (which represent experimentally observed post-stimulus beta rebound) completes the loading process. Thus, our model shows that memory gating is a two-step process where both the gamma-modulation of the input stimulus, and a subsequent external beta-entrainment of D-population are required in our model to successfully load information into working memory. Additionally, our model intrinsically reproduces several other features of persistent delay activity seen during working memory tasks, e.g. increase of gamma and beta power during the delay period.
1. FUNAHASHI, S., BRUCE, C. J. & GOLDMAN-RAKIC, P. S. 1989. *J Neurophysiol,* 61**,** 331-49. 2. WIMMER, K., RAMON, M., PASTERNAK T., COMPTE A. 2016. *J Neurosci,* 36(2), 489-505. 3. LUNDQVIST, M., ROSE, J., HERMAN, P., BRINCAT, S., BUSCHMAN, T., MILLER, E. 2016. *Neuron*, 90, 1-13. 4. HANSEL, D. & MATO, G. 2013. . *J Neurosci,* 33**,** 133-49.
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**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 520.20/TT53

**Topic:** H.01. Animal Cognition and Behavior

**Support:** 2013-2015 PICT 2012-1519

**Title:** Exploring the limits in learning capabilities of biologically plausible neural networks performing in a serial reversal task

**Authors: C. J. MININNI**[1], *B. S. ZANUTTO[2]
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**Abstract:** It has been proposed that animals construct models of their environment to better adapt their behaviour and increase their chances of survival. To achieve this goal, animals have to search for patterns even when the adaptive value of a behavioural responses not only depends on the current scenario, but also in the history of events. In this regard, the Serial Reversal Task (SRT) is a behavioural paradigm in which two rules alternate over time, demanding the animal to keep track of previous events in order to maximize reward. Traditional neural network models cannot explain learning in the SRT because learning of one rule usually erases previously acquired information. The goal of this work is to find the essential properties required by stochastic spiking neural networks to solve a SRT. We found that the SRT cannot be solved if the integration of stimulus information and the decision process occur in the same neural population. This limitation is independent of the number of neurons, neuronal dynamics or plasticity rules, and stems from the fact that plasticity is locally computed at each synapsis, and that all stimulus/response pairings are equally reinforced. We propose a biologically plausible neural network model which solves the SRT, based on separating the function of integration of stimulus information from the function of response selection. The results shed new light about the functioning of decision-making brain structures like the prefrontal cortex, and highlight the importance of characterizing neural circuits based on their connectivity and the degree of plasticity modulation with the reward.

**Disclosures: C.J. Mininni:** None. **B.S. Zanutto:** None.

**Poster**

**520. Modeling Cognitive Impairments: Mechanistic Insights and New Interventions**

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**Support:** K01MH106824

NARSAD Young Investigator

Nellie Ball Research Trust

Iowa Neuroscience Institute

**Title:** Cerebellar D1DR-expressing neurons modulate the frontal cortex during timing tasks

**Authors: K. HESLIN**[1], K. WALSH[1], Y. KIM[2], E. CARLSON[4], *K. L. PARKER[3]
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**Abstract:** The cerebellum plays an integral role in cognitive function both in the lateral cerebellar nuclei (LCN) and through its interactions with the frontal cortex. A subset of neurons in the LCN express D1 dopamine receptors (D1DRs) that are thought to be involved in cognitive processes. The precise role of these neurons remains unknown. Here we investigate how D1DR-expressing neurons in the LCN influence cognition and neuronal activity in the frontal cortex and cerebellum. Timing requires executive processes such as working memory, attention, and planning and is known to rely on both the frontal cortex and cerebellum making it an optimal task to probe cognition. We use an interval timing task where animals estimate the passage of a period of several seconds by making lever presses for a water reward. We have previously shown that a cue-evoked burst of low-frequency activity signals ramping activity, or monotonic increases or decreases, of firing rate over time in single neurons in the frontal cortex and cerebellum. These patterns of activity are essential for efficient interval timing performance. Here we explored how blocking LCN D1DRs using microinfusions of D1 dopamine antagonist SCH23390 influences timing and neural activity in the frontal cortex and cerebellum. We report that blocking LCN D1DRs impairs interval timing performance. Additionally, ramping activity and low-frequency rhythms were significantly attenuated in both the medial frontal cortex and cerebellum. These data provide insight into how the cerebellum influences medial frontal networks and the role of cerebellar dopamine in cognitive processing.

**Disclosures: K. Heslin:** None. **K. Walsh:** None. **Y. Kim:** None. **E. Carlson:** None. **K.L. Parker:** None.

**Poster**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant DA033674

NIH Grant NS092716

**Title:** Role of endocannabinoids during generalization of habituation between non-nociceptive and nociceptive pathways

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**Abstract:** Repetitive non-nociceptive stimulation is known to reduce the perception of painful stimuli and is the basis for transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS) therapies. How such stimuli produce long-lasting decreases in nociceptive signaling is poorly understood. We hypothesize that decreases in nociception following repetitive non-nociceptive stimulation represents a form of habituation, a simple form of learning in which an animal learns to de-emphasize responses to repeated or redundant stimuli. Specifically, we propose that repetitive non-nociceptive stimulation results in generalization or transfer of habituation to the nociceptive stimulus-response pathway. Following habituation training using non-nociceptive stimuli (von-Frey fibers), responses to noxious thermal stimuli (Hargreaves apparatus) were reduced in *Hirudo verbana* (the medicinal leech). Previous physiological studies in *Hirudo* have shown that repetitive stimulation of non-nociceptive afferents produces synaptic depression in nociceptive synapses that is mediated by endocannabinoid transmitters acting on a TRPV-like receptors. Consistent with these findings, injection of tetrahydrolipstatin (THL), which blocks synthesis of the endocannabinoid 2-arachydonoylglycerol (2-AG), prevented transfer of habituation from the non-nociceptive to the nociceptive pathway. Injection of the TRPV1 receptor antagonist, SB336719 (SB), also prevent transfer of habituation. Neither THL nor SB affected habitation to the non-nociceptive stimulus itself. Next, the duration of this habituating effect was examined. Surprisingly, this anti-nociceptive effect lasted longer (at least 6 days) following one block of habituation training compared to four blocks of spaced habituation training (1 day). Injection of THL and SB blocked this persistent habituation effect indicating that this long-lasting memory required TRPV and 2-AG. Preliminary studies indicate that 2-AG/TRPV signaling is required for acquisition of the habituation memory, but not its maintenance. These findings support the idea that habituation learning mechanisms contribute to the anti-nociceptive effects of repetitive non-nociceptive stimulation and may have implications for the application of TENS or SCS therapies to treat clinical pain conditions.

**Disclosures: A.D. Hanson:** None. **B.D. Burrell:** None.

**Poster**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** BBSRC (Grant Ref: BB/K018515/1)

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**Title:** Lapses during memory consolidation provide opportunities for memory replacement

**Authors: M. CROSSLEY**[1], F. LORENZETTI[2], N. SOUVIK[2], M. O'SHEA[2], *P. R. BENJAMIN[3], I. KEMENES[1]
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**Abstract:** Temporary lapses in memory recall during consolidation of long-term memory have been observed in many species, including humans, raising questions about their function in the phenomenon of memory lability. Our previous experiments suggested that lapses might represent windows of opportunity for one memory to be replaced by another. To examine this hypothesis, we induced a primary memory and then examined the effects of the formation of a second memory. We found that ability to induce memory replacement depended on the timing of the second training. When the secondary training is applied at the lapse points of primary consolidation, a secondary long-term memory was formed and the primary memory was lost. When applied at non-lapse points the primary memory persists and the secondary memory was not formed. Electrophysiological experiments in the isolated nervous system provide a systems level substrate for memory replacement and a cellular mechanism for memory maintenance.

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**Poster**

**521. Invertebrate Learning and Memory**

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**Program#/Poster#:** 521.03/TT57

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSERC

**Title:** Genetic, cellular, and behavioral dissociations of associative learning and sensory integration in *Caenorhabditis elegans*

**Authors: *G. S. WOLFE**[1], V. W. TONG[1], D. MERRITT[1], G. W. STEGEMAN[2], S. FLIBOTTE[3], D. VAN DER KOOY[4]
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**Abstract:** The mechanisms of learning and memory can be studied by taking advantage of model organisms such as *Caenorhabditis elegans*. We have characterized an EMS derived mutant strain, *lrn-2,* which shows deficits in both sensory integration and a wide variety of associative learning paradigms. Mapping, sequencing, complementation tests and wild type gene rescue have localized this mutation to the gene *scd-2.* The primary assay of sensory integration involved overcoming an aversive copper barrier to reach an attractive diacetyl odorant. The primary learning assay involved associating the pathogenicity of *P. aeruginosa* bacteria with its odor. We have shown that sensory integration and associative learning can be dissociated at three different levels of investigation and thus predict that behavioral responses to sensory integration and associative learning are driven by separately encoded representations of sensory cues within the worm "mind". There is dissociation at the genetic level because we have demonstrated that sensory integration and associative learning use separate molecular pathways. While *scd-2* is downstream of *fsn-1*, a gene that produces part of a ubiquitination complex, in the sensory integration pathway, we performed epistasis experiments showing that *scd-2* has a different epistatic relationship with *fsn-1* in associative learning. There is dissociation of the neuronal circuits driving sensory integration and associative learning. While sensory integration requires expression of *scd-2* in AIA interneurons, associative learning uses a different neuronal pathway, likely involving NSM serotonergic neurons. Finally, we have shown that *scd-2* mutants can fail at integrating copper and diacetyl cues while simultaneously successfully forming an associative memory of the same cues. This was demonstrated by testing *scd-2* mutant behavioral response to copper after initial exposure to copper paired with diacetyl. While mutants could not initially cross a copper barrier to reach diacetyl, this exposure led to an increased attraction to copper, indicative of an association between the two cues. These experiments demonstrate a dissociation between sensory integration and associative memory. Even though both psychological processes require detection of sensory cues followed by a modified behavioral response, they require separate genetic and cellular pathways, and can occur both simultaneously and independently from each other.

**Disclosures: G.S. Wolfe:** None. **V.W. Tong:** None. **D. Merritt:** None. **G.W. Stegeman:** None. **S. Flibotte:** None. **D. van der Kooy:** None.

**Poster**

**521. Invertebrate Learning and Memory**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** RSF Grant 14-25-00072

**Title:** Nitric oxide erases/destabilizes existing memory during reconsolidation in snails and rats

**Authors: *P. M. BALABAN**, M. RYSAKOVA, A. VINARSKAYA, V. IVANOVA, A. ZUZINA, N. BAL
Inst. Higher Nervous Activity & Neurophysiol. RAS, Moscow, Russian Federation

**Abstract:** It is well known that reactivation of consolidated fear memory under boundary conditions of novelty and protein synthesis blockade results in an impairment of memory, suggesting that the reactivated memory is erased/destabilized and requires synthesis of new proteins for successful reconsolidation. The role of nitric oxide (NO) in the development of memory was repeatedly described in a range of animal models. Recently in terrestrial snails it was shown that contextual fear memory was significantly impaired 24 hrs after memory reactivation under injection of a protein synthesis blocker anisomycin (ANI), but similar reactivation of memory under a combined injection of ANI and a range of NO-synthase inhibitors (or the NO scavenger) demonstrated absence of impairment of the long-term contextual memory. Blockade of NO prevented erasure/destabilization of long-term memory. These results evidence that NO is involved in the destabilization (erasure) of a consolidated context memory in mollusks (Balaban *et al.*, 2014). In the present work, we tested the hypothesis of the NO involvement in memory destabilization during the reconsolidation process in rats using memory reactivation under different conditions. We report that administration of NO-synthase selective blockers 3-Br-7-NI or ARL in the conditions of reactivation of memory under a protein synthesis blockade prevented destabilization of fear memory to the conditioned stimulus. Obtained results support the role of NO signaling pathway in the destabilization of existing fear memory triggered by reactivation, and demonstrate that the disruption of this pathway may prevent memory reactivation-induced changes in long-term memory. It was suggested that the mechanism of memory destabilization either may be a direct local S-nitrosylation of the peptides participating in memory maintenance, or may be triggering of the proteasomal degradation of proteins by NO. We investigated influence of endogenous nitric oxide production on proteasomal protein degradation. We have shown that nitric oxide synthase blockade prevents decline of the GFP-based proteasomal protein degradation reporter in neuronal processes of the hippocampal primary culture. It suggests that nitric oxide may regulate ubiquitin-dependent proteasomal protein degradation in neurons. Obtained results suggest that nitric oxide is involved in the protein degradation in proteasomes in physiological conditions.

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**Poster**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSERC RGPIN Grant 8319

**Title:** Kamin blocking in *C. elegans* may be due to perceptual interference rather than memory storage

**Authors: *D. M. MERRITT**[1], J. G. MELKIS[2], B. KWOK[1], C. TRAN[1], D. VAN DER KOOY[1]
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**Abstract:** Higher-order conditioning phenomena, including context conditioning and blocking, occur when conditioning to one set of stimuli interacts with conditioning to a second set of stimuli to modulate the strength of the resultant memories. In blocking, a first conditioned stimulus (CS1), when associated with an unconditioned stimulus (US), prevents subsequent learning of a second conditioned stimulus (CS2) to the US when trained in the presence of CS1. In context conditioning, association of a CS to the US is recalled only when tested in a context similar to that it was learned in. Here we analyze these phenomena in the nematode worm *Caenorhabditis elegans*, demonstrating for the first time the presence of blocking in this animal, and identifying conditions that behaviorally dissociate it from simultaneous context conditioning. We present an initial genetic dissection of context conditioning and blocking in a model benzaldehyde/$NH_4Cl$ aversive learning paradigm, and demonstrate that blocking occurs independent of retrieval of CS1, but dependent on its sensation, and that at least the initial stages of the CS2 memory are formed even in blocking conditions. While traditional explanations of blocking posit that storage of the CS2 memory is impaired in situations in which the US is already predicted by CS1, our findings suggest a fundamentally different explanation. We propose that blocking may work to interfere with subsequent retrieval of the CS2 memory in *C. elegans*, rather than interfering with its storage, and that this process occurs independent of retrieval of the CS1 memory during CS2 training - that is, that CS1 prediction of the US is not required for CS2 blocking. Our findings suggest a fundamental reinterpretation of blocking, and position *C. elegans* as a powerful model organism for the study of higher order conditioning.

**Disclosures: D.M. Merritt:** None. **J.G. Melkis:** None. **B. Kwok:** None. **C. Tran:** None. **D. van Der Kooy:** None.

**Poster**

**521. Invertebrate Learning and Memory**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant, (NIA, 1R15AG045820-01A1)

**Title:** Dactylobiotus dispar as a model organism to study the metabolic necessity for memory storage

**Authors: S. Y. ZHOU**, P. M. DWIVEDY, J. P. DEFRANCO, D. M. ZIMMET, M. MAGDITS, *T. C. DUMAS
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**Abstract:** Tardigrades, also known as water bears, are microscopic eight-legged animals that live in various aquatic and terrestrial environments. They are known for their resilience to extreme conditions due to their ability to enter cryptobiosis. This rare property presents an opportunity to explore principle components of memory storage; for instance, does the storage of memories require ongoing metabolism or can they be stored purely in structure? Thus, the purpose of this project is to use tardigrades to determine metabolic necessity for memory storage. Dactylobiotus dispar tardigrades were trained in a delayed fear conditioning paradigm to associate a blue light (conditioned stimulus) with a mild shock (unconditioned stimulus). Following pairing, the animals display the conditioned response (curling) upon presentation of the blue light only, reflecting a learned association between the blue light and the shock. To confirm that this was associative learning, various control experiments are performed (shock only, blue light only, reverse pairing). Animals are being conditioned multiple times to produce long-lasting memories. Half of these animals will undergo cryptobiosis (tunning), while the other half does not. Upon revival, the tunned tardigrades will be compared to the control tardigrades with respect to memory integrity and duration. If fear conditioning memories rely on metabolism, then memory performance is expected to be impaired in the tunned animals. However, if memory storage does not rely on metabolism, then no difference in memory performance should occur. Finally, tunned tardigrades might show improved memory performance due to a stasis effect on memory decay. We are also developing methods to rapidly and reliably tun and revive this species of tardigrades. This research opens a new area of neurobiology may provide a new perspective on the neural bases of learning and memory.

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**Poster**

**521. Invertebrate Learning and Memory**

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No. 15JC1400102 to L.L.

NSFC 81327802 to S.Z. and Y. Liu

**Title:** A distinct entorhinal cortex to hippocampal CA1 direct circuit for olfactory associative learning

**Authors: *Y. LI**[1], J. XU[2], Y. LIU[3], J. ZHU[1], N. LIU[4], M. RASCH[4], C. LI[1], S. ZENG[3], L. LIN[2], X. ZHANG[4]
[1]Inst. of Neuroscience, CAS, Shanghai, China; [2]Key Lab. of Brain Functional Genomics-Ministry of Education, Sch. of Life Science, East China Normal Univ., Shanghi, China; [3]Huazhong Univ. of Sci. & Technol., Wuhan, China; [4]State Key Lab. of Cognitive Neurosci. & Learning and IDG/McGovern Inst. for Brain Research, Beijing Normal Univ., Beijing, China

**Abstract:** Lateral and medial parts of entorhinal cortex (EC) convey nonspatial ‘what’ and spatial ‘where’ information, respectively, into hippocampal CA1, via both the indirect EC layer 2→ hippocampal dentate gyrus→CA3→CA1 and the direct EC layer 3→CA1 paths. However, it remains elusive how the direct path transfers distinct information and contributes to hippocampal learning functions. Here we report that lateral EC projection neurons selectively form direct excitatory synapses onto a subpopulation of morphologically complex, calbindin-expressing pyramidal cells (PCs) in the dorsal CA1 (dCA1), while medial EC neurons uniformly innervate all dCA1 PCs. Optogenetically inactivating the distinct lateral EC-dCA1 connections or the postsynaptic dCA1 calbindin-expressing PC activity slows olfactory associative learning. Moreover, optetrode recordings reveal that dCA1 calbindin-expressing PCs develop more selective spiking responses to odor cues during learning. Thus, our results identify a direct lateral EC→dCA1 circuit that is required for olfactory associative learning.

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**Poster**

**521. Invertebrate Learning and Memory**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** Korea Institute of Science and Technology (Brain Research Institute)

**Title:** Expression patterns of DD2R in different dopaminergic neuronal clusters and its role in *Drosophila* larval olfactory learning

**Authors: *C. QI**, D. LEE
Biol., Ohio Univ., Athens, OH

**Abstract:** Dopamine (DA) plays a critical role in conditional learning via interacting with two receptor subfamilies: excitatory D1- and inhibitory D2-like receptors. In *Drosophila melanogaster*, postsynaptic D1 receptors are known to be involved in associative olfactory learning in both adults and larvae. However, whether modulation of synaptic DA release by presynaptic D2 autoreceptors plays a crucial role in olfactory learning is still unknown.
In addition to DA receptors, different DA neural circuits are involved in different olfactory learning (i.e. appetitive and aversive). Former studies showed in larval brains, dopaminergic neurons (DAN) in the dorso-lateral 1 (DL1) cluster innervating into the vertical lobe of mushroom body (MB) are necessary for aversive olfactory learning, while DANs in the primary protocerebral anterior medial (pPAM) clusters innervating into the medial lobes of MB are important for appetitive learning. Based on this, we aimed to examine whether *Drosophila* Dopamine 2 Receptors (DD2R) are expressed in different DA neuronal clusters (i.e. DL1 vs pPAM), and whether these DD2Rs are involved in different *Drosophila* olfactory learnings.
By using a GFP-tagged DD2R strain, the expression patterns of DD2R were explored in DANs (including pPAM and DL1). To investigate the role of DD2R in distinct DANs, we drove expression of DD2R-RNAi under distinct DAN-specific drivers. The olfactory learning assay showed aversive learning is totally impaired in larvae with DD2R knockdown under TH-GAL4 driver (including DL1, but not pPAM), while the appetitive learning is partially impaired. This is consistent with our results of DAN-to-MB GRASP (split-GFP Reconstitution Across Synaptic Partners) using TH-GAL4: more intensive GRASP signals were observed in the vertical lobes than those in the medial lobes, showing more functional synapses between DANs and vertical lobes of MB. These results demonstrated DD2Rs in the DANs under TH-GAL4 have an important role in larval aversive learning. On the other hand, knockdown of DD2R under a pPAM-specific driver (R58E02-GAL4) totally impaired appetitive learning, which indicates DD2Rs in pPAM clusters have an important role in appetitive learning. Our findings revealed DD2R auto-receptors in distinct DAN clusters have different functions in *Drosophila* larval olfactory learning. To investigate possible mechanisms of DA mediated learning, we are currently studying how DD2R knockdown induced impaired olfactory learning at the level of synaptic neurotransmission.

**Disclosures: C. Qi:** None. **D. Lee:** None.

**Poster**

**521. Invertebrate Learning and Memory**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant NS088835

**Title:** Inhibition of protein degradation enables the induction of associative memory following sleep deprivation

**Authors: E. J. NOAKES**, H. C. KRISHNAN, *L. C. LYONS
Dept. of Biol. Science, Program in Neurosci., Florida State Univ., Tallahassee, FL

**Abstract:** Sleep deprivation and sleep disorders constitute a significant public health problem in the United States and worldwide. Sleep deprivation results in cognitive and performance impairments in adolescents and adults. Though recent research has begun to uncover the molecular mechanisms through which sleep deprivation impacts memory formation, a clear understanding has yet to emerge. The marine mollusk *Aplysia californica*, with its well-established learning paradigms and diurnal consolidated sleep pattern (Vorster et al., 2014), represents an excellent model for investigating the interaction of sleep and memory. *Aplysia* exhibit decreased responsiveness to sensory stimulation during sleep and rebound sleep following nine hours sleep deprivation (Vorster et al., 2014). Recently, we demonstrated that acute and chronic sleep deprivation inhibit the induction of short and long-term operant memory formation using the learning that food is inedible paradigm (Krishnan et al., 2016). As research in mice suggests that sleep deprivation impairs memory consolidation through the suppression of protein synthesis (Tudor et al., 2016), we hypothesized that sleep deprivation may affect the induction of memory through an imbalance in protein synthesis and protein degradation. Previously, we demonstrated that maintenance of steady state protein levels through dual inhibition of protein synthesis and protein degradation permitted long-term memory formation (Lyons et al., 2016). If sleep deprivation affects protein regulation through either decreased protein synthesis or increased protein degradation, then potentially inhibiting protein degradation may restore conditions to permit the induction of memory. To test whether the inhibition of protein degradation mitigates the effects of sleep deprivation on memory, animals were sleep deprived for nine hours using contextual changes and tactile stimulation and injected with the proteasome inhibitor MG-132 or vehicle three hours prior to the end of sleep deprivation. Animals were then trained using the learning that food is inedible paradigm 1 h following sleep deprivation and tested either 30 minutes later for short-term memory or 24 hours later for long-term memory. Remarkably, MG-132 treated animals exhibited robust short-term and long-term memory while the vehicle treated animals failed to show any memory. These results suggest that sleep deprivation may inhibit the induction of memory through misregulation of the balance of protein synthesis and protein degradation.

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**Poster**

**521. Invertebrate Learning and Memory**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** CEES Grant, Wake Forest University

**Title:** Chronic and acute exposure of honey bees to fipronil reduces synaptic density in the mushroom bodies

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**Abstract:** Fipronil, a commonly used insecticide, is a GABA receptor antagonist that induces hyperexcitability in the central nervous system of insects. Its use is controversial because it is a suspected contributor to the global decline of non-target pollinator populations. Sublethal doses of fipronil reduce colony fitness and impair learning and memory in the honey bee, *Apis mellifera*. The mushroom bodies (MB), insect brain regions required for learning and memory, receive GABAergic inputs that may be sensitive to fipronil. The synaptic organization of the MB was investigated in adult worker honey bees exposed to fipronil as larvae and/or as adults using immunolabeling of the pre-synaptic marker anti-synapsin I and laser scanning confocal microscopy. This permits the visualization of synaptic complexes called microglomeruli. Exposure to fipronil at field-realistic (1 ppb), as well as low (0.1 ppb) and high (4 ppb) concentrations decreased the density of microglomeruli in the MB lip (olfactory) and collar (visual) regions in adult- and larval-treated honey bees. These data indicate that sublethal doses of fipronil alter the structure of the adult honey bee nervous system, possibly through induced synaptic pruning. These results potentially link impaired learning with abnormal synaptic organization, suggesting a mechanism by which fipronil reduces the fitness of honey bee foragers and, ultimately, colonies.

**Disclosures: J.J. Privitt:** None. **S.E. Fahrbach:** None.

**Poster**

**521. Invertebrate Learning and Memory**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 521.11/TT65

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Israel Science Foundation Grant 1379/12

**Title:** Molecular correlates of components of training with inedible food in *Aplysia*

**Authors: V. LUCHINSKY-BRISKIN**, R. LEVY, I. HURWITZ, *A. J. SUSSWEIN
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**Abstract:** Many combinations of stimuli and responses may be experienced while learning. These may affect different regions of the nervous system, and can trigger different molecular cascades. We used learning that food is inedible in *Aplysia* to determine which aspects of a complex training paradigm produce changes in expression of different genes in different ganglia. Memory that a food is inedible in *Aplysia* arises from 3 contingent stimuli: 1) food stimulating the lips; 2) attempts to swallow; 3) failure to enter the gut. Training animals until they stop responding takes 15-20 min, and produces both short- and long-term memories. Treatment with an NO donor substitutes for failed attempts to swallow: lip stimulation for 15-20 min paired with an NO donor produces 24 h memory. Stopping the training after 3 min is ineffective in producing 24 h memory. However, a 3 min training paired with an NO donor produces 24 h memory. A 3 min lip stimulation paired with an NO donor produces no memory.
To dissect molecular correlates of different components of training, we examined changes in mRNA expression after a 3 min training, either paired or unpaired with an NO donor, and of a 3 min lip stimulation, paired or unpaired with an NO donor. A 3 min training (independent of the NO donor) produced increases in mRNA expression of C/EBP, CREB1, CREB1α and of CREB1β in the buccal but not cerebral ganglia. This is consistent with previous findings that localized molecular correlates of training to the buccal ganglia. The NO donor (independent of training) produced increases of the same 4 mRNAs, and of sensorin, in the buccal ganglia, and also produced increases in these 4 mRNAs, and of CREB2 in the cerebral ganglion. The extensive changes in gene expression produced by the NO donor alone in the cerebral ganglion suggests that the primary site at which NO affects memory formation may be in the cerebral ganglion, perhaps on targets of nitrergic neuron C2.
For C/EBP and CREB1 in the buccal ganglia, increases after a 3 min training plus the NO donor were the sum of the increases produced by each stimulus alone. For CREB1α and CREB1β increases after 3 min training plus the NO donor were larger than the sum of the individual increases, indicating that these increases are a correlate of memory formation.

**Disclosures: V. Luchinsky-Briskin:** None. **R. Levy:** None. **I. Hurwitz:** None. **A.J. Susswein:** None.

**Poster**

**521. Invertebrate Learning and Memory**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 521.12/TT66

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH grants MH096120

NIH NS029563

NSF IOS 1121690

**Title:** Partial training requires protein synthesis to reverse amnesia produced by posttraining protein synthesis inhibition in *Aplysia*

**Authors: K. PEARCE**[1], D. CAI[1], S. CHEN[1], S. APICHON[1], B. CHEEMA[1], D. MIRESMAILI[1], R. SUMNER[1], A. RANGCHI[1], A. ZOBI[1], *D. L. GLANZMAN[2,3]
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**Abstract:** Previously, we reported that the long-term memory (LTM) for behavioral sensitization in *Aplysia* can be reinstated by abbreviated (partial) training following its disruption by reconsolidation blockade or inhibition of PKM (Chen et al., 2014). Recently, we found that LTM can be induced by partial training after disruption of memory consolidation by protein synthesis inhibition (PSI) begun shortly after training (Pearce et al., 2017). Here, we asked: What are the molecular and cellular processes recruited by partial training that reverse the retrograde amnesia caused by posttraining PSI? To address this question, we first disrupted original memory consolidation by injecting anisomycin, a protein synthesis inhibitor, into animals shortly after full sensitization training; we then tested whether a second injection of anisomycin, prior to or immediately after, partial training disrupted the induction of LTM. The initial, full sensitization training consisted of five spaced bouts of electrical shocks (5X training) delivered to the tail via implanted electrodes. Immediately after the 5X training, either anisomycin or vehicle solution was injected into the hemocoel of the animals. After a posttraining test at 24 h, some animals received partial sensitization training, which consisted of three spaced bouts of tail shocks (3X training). A second injection of anisomycin/vehicle solution was given prior to, or immediately after, the partial training. As previously reported, we found that LTM was fully induced by partial training following retrograde amnesia produced by anisomycin treatment begun shortly after 5X training. But inhibition of protein synthesis, either during or shortly after partial training, blocked the ability of partial training to reverse the retrograde amnesia. Our data indicate that partial training reverses the amnestic effects of posttraining PSI on original sensitization memory through a protein synthesis-dependent process.

**Disclosures: K. Pearce:** None. **D. Cai:** None. **S. Chen:** None. **S. Apichon:** None. **B. Cheema:** None. **D. Miresmaili:** None. **R. Sumner:** None. **A. Rangchi:** None. **A. Zobi:** None. **D.L. Glanzman:** None.

**Poster**

**521. Invertebrate Learning and Memory**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 521.13/UU1

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant SC3GM111188

**Title:** Modulation of learning-induced long-term behavioral plasticity by prolonged food deprivation and extended sensitization training in *Aplysia*

**Authors: *R. MOZZACHIODI**, K. MAC LEOD, A. SEAS, M. L. WAINWRIGHT
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**Abstract:** Following exposure to aversive stimuli, an organism budgets its behaviors by augmenting defensive responses and suppressing non-defensive behaviors. However, this process must be flexible to accommodate modifications in the animal's internal and/or external state that require the normal balance between defensive and non-defensive behaviors to be adjusted. For example, the mollusk *Aplysia* budgets its behaviors by concurrently enhancing defensive withdrawal reflexes (i.e., sensitization) and suppressing feeding, when exposed to noxious stimuli. In particular, sensitization and feeding suppression are co-expressed across different training protocols and share common temporal domains, suggesting that they are interlocked.

This project focused on the co-expression of the long-term sensitization and feeding suppression and aimed to "uncouple" them using: 1) manipulation of the animal's motivational state through prolonged food deprivation and 2) extended training that induces sensitization lasting for weeks. First, we examined the effects of 14-day food deprivation on the long-term (24 h) co-expression of sensitization and feeding suppression that is commonly induced by a 4-trial training protocol (ITI: 30 min). Four groups of animals were included: trained/14-day food deprived (T-14), untrained/14-day food deprived (UT-14), trained/2-day food deprived (T-2) and untrained/2-day food deprived (UT-2). For each group, the duration of the tail-induced siphon withdrawal reflex (TSWR) and the number of bites in response to a food stimulus were measured prior to and 24 h after training. Sensitization was absent in T-14 animals, whereas it was observed in T-2 animals. Interestingly, feeding suppression was significantly reduced in T-14 animals, when compared to T-2 animals, but it was not completely abolished.

Second, we employed an extended training protocol (4 trials per day x 4 consecutive days) to determine whether feeding remained suppressed as long as sensitization was expressed. The TSWR duration and the number of bites were measured prior to and at 24 h, 72 h and one week in trained and untrained animals. A dissociation between the expression of sensitization and feeding suppression occurred: feeding suppression and sensitization were co-expressed only at the 24-h time point. Feeding suppression was no longer observed at 72 h or later, while sensitization was still present one week after training.

These findings indicate that sensitization and feeding suppression are not interlocked and that their long-term co-expression can be altered by internal (prolonged food deprivation) and external (extended aversive training) factors.

**Disclosures: R. Mozzachiodi:** None. **K. Mac Leod:** None. **A. Seas:** None. **M.L. Wainwright:** None.

**Poster**

**521. Invertebrate Learning and Memory**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 521.14/UU2

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grants R01NS019895

**Title:** Role of ribosomal S6 kinase (RSK) in long-term facilitation (LTF) at sensorimotor (SN-MN) synapses of *Aplysia*

**Authors: *R.-Y. LIU**, L. J. CLEARY, J. H. BYRNE
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**Abstract:** Coffin-Lowry syndrome (CLS), a type of cognitive disorder that is associated with deficits in learning and memory, is caused by X-linked mutations in the ribosomal S6 kinase 2 (RSK2) gene (Delaunoy et al. 2006). In vertebrates, RSK is activated by ERK and phosphorylates CREB. Although the RSK2 gene has been identified in *Aplysia*, and serotonin (5-HT) appears to activate RSK via the ERK pathway (Philips et al. 2013), the RSK signaling cascades and their roles in long-term synaptic facilitation (LTF) have not been completely examined. In the present study, we used immunocytochemistry to measure the phosphorylation of RSK and found that a standard repeated treatment with 5-HT enhanced phosphorylation of RSK in isolated sensory neuron (SN) cultures. This effect was attenuated by the MEK inhibitor U0126, indicating that it depended upon the MEK-ERK pathway. Moreover, U0126 attenuated 5-HT-induced phosphorylation of CREB1. These results suggest an important role for RSK in the induction of LTF. Next, we targeted this protein using siRNA knockdown, and determined the effect of decreasing RSK expression on CREB1 phosphorylation and LTF. RSK protein levels were assayed by immunofluorescence 96 h after injection of either RSK siRNA or scrambled-siRNA (Con siRNA). RSK protein levels in the SNs injected with RSK siRNA were 28 ± 6.0 % less than those in Con siRNA injected SNs. Moreover, in the SNs injected with RSK siRNAs, 5-HT-induced increases in pCREB1 levels were reduced 31 ± 5.6 %, compared to the Con siRNA-injection group. Finally, injection of RSK siRNA into SNs of SN-MN co-cultures resulted in a significant reduction of LTF (changes in EPSP at 24 h after 5-HT: Con siRNA 90 ± 24 %; RSK siRNA 16 ± 5.6 %). These data suggest that RSK is required for the induction of LTF. Our results suggest that the isolated sensory neuron is an effective system to investigate methods for restoring RSK-related deficits in neuronal function that may occur in CLS.

**Disclosures: R. Liu:** None. **L.J. Cleary:** None. **J.H. Byrne:** None.

**Poster**

**521. Invertebrate Learning and Memory**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 521.15/UU3

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant R01 NS019895

**Title:** Biphasic regulation of p38 MAPK by serotonin in *Aplysia* sensory neurons

**Authors: *Y. ZHANG**, P. SMOLEN, D. A. BAXTER, J. H. BYRNE
McGovern Med. Sch. of UTHSC At Houston, Houston, TX

**Abstract:** Mitogen-activated protein kinase (MAPK) pathways play critical roles in mediating diverse forms of synaptic plasticity. In *Aplysia*, the ERK isoform is required for long-term synaptic facilitation (LTF), whereas the p38 MAPK isoform is required for long-term synaptic depression (LTD). To better understand the roles of ERK and p38 MAPK, we previously quantified the dynamics of their activation and investigated their interactions (Zhang et al. 2017; ENEURO.0373-16.2017). Following a single 5-min pulse of 5-HT, ERK activity peaked ~45 post-treatment and returned to basal levels by 60 min post-treatment, consistent with results in Philips et al. (2013). In contrast, 5-HT induced a transient inhibition of p38 MAPK, followed by a delayed activation between 25 and 45 min, and a return to basal level at 60 min. Finally, a MAPK kinase inhibitor (U0126) blocked activation of both ERK and p38 MAPK and a p38 MAPK inhibitor (SB203580) blocked the decrease in ERK activity. These data indicate complex interactions between the two pathways. Here, we examined the activity of p38 MAPK at different times after five pulses of 5-HT with regular interstimulus intervals (ISIs) of 20 min. Biphasic regulation of p38 MAPK activity was observed, with a late phase of activation emerging hours after treatment. Compared to vehicle control measurements at the same time points, phosphorylated p38 MAPK (p-p38 MAPK) was elevated by +22.4 ± 6.2% (n = 7) at 1 h after treatment, followed by a decrease to -13.3 ± 9.7% (n = 6) 2 h after treatment. A second increase in p-p38 MAPK levels was evident at 5 h (+15.9 ± 8.9%, n = 6), and p-p38 MAPK levels were also elevated at 24 h (+8.3% ± 6.5%, n = 6). These results indicate that p-p38 MAPK exhibits complex dynamics that could have profound consequences on the effectiveness of different training protocols employed to induce LTF and LTM.

**Disclosures: Y. Zhang:** None. **P. Smolen:** None. **D.A. Baxter:** None. **J.H. Byrne:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.01/UU4

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSERC CGS D

OGS

Restracomp

**Title:** Visualizing a lateral amygdala engram

**Authors: *E. KRAMER**[1], J. R. EPP[2], P. W. FRANKLAND[3], S. A. JOSSELYN[4]
[2]Program in Neurosciences and Mental Hlth., [3]PGCRL - NMH 5th floor, [4]Neurosci. & Mental Hlth., [1]Hosp. For Sick Children, Toronto, ON, Canada

**Abstract:** An engram or memory trace may be defined as the neural substrate of stored information that results from past experience and bestows organisms with the ability to express memory in their behaviour. Previous research implicates the amygdala, in particular the lateral nucleus of the amygdala (LA), in encoding and storing associative fear memories. To image the memory trace, previous research relied on the use of antibodies directed against immediate early genes (IEGs; e.g., c-Fos, Arc, etc.). In traditional methods, tissue must be prepared in thin slices, and therefore the three-dimensional aspect of an engram is lost. To observe molecular markers of neuronal activity throughout the LA, we have developed a method to tag and image a fear memory engram in intact, three dimensional tissue. Tissue is processed using a modified Clear Lipid-exchanged Anatomically Rigid Imaging/immunostaining-compatible Tissue hYdrogel (CLARITY) protocol, where samples are embedded in a fixative solution with low hydrogel concentration and passively cleared using detergent before RNA fixation. Small probes are hybridized to the IEG *Arc* and *Homer1a*, and signal is amplified using hybridization chain reaction, where fluorescently tagged nucleic acid hairpin sequences self-assemble into detectable fluorescent polymers. Expression of each IEG allows for identification of neurons active 5 min, and 30 min before sacrifice. Samples are then imaged with either confocal or light-sheet microscopy and processed for detection of nuclei and IEG signal in 3D. We then use this data to examine the number and spatial distribution of neurons that are required to encode and recall memories. This technique allows for the observation of an LA engram in its entirety, and can allow for examination of engram properties in three dimensions. Further analysis will allow us to compare the specific neural signals of memory to behavioural expression of memory recall in mice.

**Disclosures:** **E. Kramer:** None. **J.R. Epp:** None. **P.W. Frankland:** None. **S.A. Josselyn:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.02/UU5

**Topic:** H.01. Animal Cognition and Behavior

**Support:** SickKids Restracomp

NSERC CGS-M

Ontario Graduate Scholarship

**Title:** Modelling the impact of new learning and neurogenesis on memory stability in the hippocampus

**Authors:** ***L. M. TRAN**[1,2], S. A. JOSSELYN[3], B. A. RICHARDS[5], P. W. FRANKLAND[4]
[1]Neurosciences & Mental Hlth., Sickkids PGCRL, Toronto, ON, Canada; [2]Physiol., Univ. of Toronto, Toronto, ON, Canada; [3]Neurosci. & Mental Hlth., [4]PGCRL - NMH 5th floor, Hosp. For Sick Children, Toronto, ON, Canada; [5]Biol. Sci., Univ. of Toronto Scarborough, Scarborough, ON, Canada

**Abstract:** In neural networks, the stability of stored information may be compromised by a) changing the neural architecture, and b) adding new memories. We tested these ideas in a three layer feed-forward neural network. In this network the input, middle and output layers represent the entorhinal cortex, DG and CA3 regions, respectively. We presented the network with input patterns, drawn from two partially overlapping distributions A and B. The network was trained to transform these A and B input patterns into one of two discrete output patterns. The ability of the network to generalize was assessed by presenting novel input patterns that were either drawn from the A and B distributions, and asking whether it could correctly categorize them. Following initial training, we either a) added new neurons to the middle layer, or b) trained the network on two new distributions, C and D. Changes in neural architecture induced by either a) new neuron addition or b) new learning impaired AB categorization performance, consistent with previous modeling and experimental data. Moreover, increasing excitability and connectivity (input and output) of the new neurons exacerbated these forgetting effects. We next examined how these factors interact. In this experiment, we trained the network on distributions A and B and then added new neurons, as above. We then retrained the network on the new distributions C and D. In this case, the addition of new neurons weakened memory for the original AB categorization, but, at the same time, enhanced learning of the new CD categorization. By exploring how new

neuron addition impacts stored memories, and new memory storage, our results begin to help us understand how adult neurogenesis in the hippocampus influences cognition.

**Disclosures: L.M. Tran:** None. **S.A. Josselyn:** None. **B.A. Richards:** None. **P.W. Frankland:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.03/UU6

**Topic:** H.01. Animal Cognition and Behavior

**Support:** CIHR Vanier

**Title:** Neurocartography: Mapping cell signals brain wide

**Authors: *P. E. STEADMAN**[1,2], J. W. KENNEY[1], A. D. JACOB[1], M. AHMED[1], J. R. EPP[1], C. YAN[1], J. P. LERCH[1], S. A. JOSSELYN[1], P. W. FRANKLAND[1]
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**Abstract:** New tissue clearing and imaging methods are allowing cellular signals to be visualized across whole intact organs. However, the datasets that emerge from these types of analyses are complex, and one major challenge is to develop efficient computational approaches that can be applied to a broad range of datasets (e.g., different clearing methods, different species etc). To date, analysis pipelines have been developed for analyzing whole brain gene expression in iDISCO-cleared mouse brains (ClearMap) and neuronal projections in CLARITY-cleared mouse brains (CAPTURE). Inspired by these tools, we have developed a robust pipeline for imaging, segmenting and analysing cellular signals across the brain that can be used in different model organisms, and following different types of clearing technique. Brain tissue from the adult mouse and zebrafish were collected and processed using either CLARITY or iDISCO clearing techniques. Cleared samples were then imaged and processed for signal quantification. Images were acquired using a commercial light-sheet microscope with parameters optimized for specific clearing and fluorophore methods. Next, image stacks were segmented automatically into distinct brain regions. This portion of the pipeline was constructed using PydPiper, a python tool for building image registration pipelines. Cellular signals were automatically quantified using a popular-vote from several classifier algorithms implemented in python. Cell signal and brain regions were then transformed into region specific cell counts and densities allowing for comparisons between experimental groups as well as between brain areas. We validated our computational approach using ground truth counts from distinct regions and a range of signal sources (i.e., reporter mouse lines and immunohistochemical signals). Finally, we apply our

pipeline to examine neural circuits engaged during fear memory formation and retrieval, and how these circuits are altered in diseased states.

**Disclosures: P.E. Steadman:** None. **J.W. Kenney:** None. **A.D. Jacob:** None. **M. Ahmed:** None. **J.R. Epp:** None. **C. Yan:** None. **J.P. Lerch:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.04/UU7

**Topic:** H.01. Animal Cognition and Behavior

**Support:** CIHR (FDN143227)

NSERC

**Title:** Identification of an inhibitory hippocampal-thalamic pathway that is necessary for remote memory retrieval

**Authors: *G. VETERE**[1], F. XIA[2], S. A. JOSSELYN[3], P. W. FRANKLAND[4]
[1]Program In Neurosci. & Mental Hlth., [3]Neurosci. & Mental Hlth., [4]PGCRL - NMH 5th floor, [2]Hosp. For Sick Children, Toronto, ON, Canada

**Abstract:** Systems consolidation requires time-dependent reorganization of brain regions that are necessary for memory retrieval. But how the memory retrieval circuits change over time is not fully understood. The anterodorsal thalamic nucleus (ADn) has been shown to be important for short-term spatial and working memory performance. However, how the role of ADn changes during systems consolidation, and its involvement in remote memory retrieval are unknown. We first show that the activity of ADn during contextual fear memory retrieval decreases over time (1 vs. 28 days post-training). While this could suggest that ADn is no longer necessary during remote memory retrieval, an intriguing alternative is that inhibition of ADn is required to allow successful retrieval at the remote time point. To explore the latter possibility, we first identified regions with monosynaptic projections to the ADn using retrograde tracers (retrobeads and fluorogold). Then we specifically labeled those projections that are inhibitory by infusing a cre-recombinase-dependent adeno-associated virus (AAV) carrying the fluorescence tag EYFP in various brain regions of VGAT-Cre mice. We identified strong inhibitory projections from CA3 to the ADn that could mediate the inhibition of ADn. To test whether this CA3-ADn inhibitory pathway is necessary for remote memory retrieval, we bilaterally infused a cre-recombinase-dependent AAV carrying the inhibitory opsin iC++ in CA3 of VGAT-Cre mice to specifically inhibit GABAergic projections from CA3 to ADn. We trained mice in contextual

fear conditioning, then inhibited the CA3-ADn projections during retrieval test. When we inhibited these projections 28 days, but not 1 day, post-training, mice showed memory deficits. These results suggest that the CA3 inhibition of ADn is required for remote memory retrieval. Our findings provide support for the time-dependent reorganization of memory retrieval circuits, and we show, for the first time, that a CA3-ADn inhibitory pathway is gradually recruited during consolidation and becomes increasingly necessary for fear memory retrieval over time.

**Disclosures: G. Vetere:** None. **F. Xia:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.05/UU8

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Natural Sciences and Engineering Research Council of Canada

Canadian Institutes of Health Research

**Title:** Temporal and circuit dynamics of memory allocation in the amygdala

**Authors: *J. YU**[1,2], A. J. RASHID[1], C. YAN[1,3], A. DE CRISTOFARO[1], P. W. FRANKLAND[1,2,3,4], S. A. JOSSELYN[1,2,3,4]
[1]Neurosciences and Mental Hlth., The Hosp. For Sick Children, Toronto, ON, Canada; [2]Physiol., [3]Inst. of Med. Sci., [4]Psychology, Univ. of Toronto, Toronto, ON, Canada

**Abstract:** In the lateral amygdala (LA), memory allocation is a competitive process governed by changes in both excitatory and inhibitory neuron activity that can occur prior to learning. While these changes can be sustained (<6h) as a result of previous experience (Rashid et al, 2016), it is not known whether transient increases in activity are also sufficient to drive the events required for allocation to occur. To characterize the time frame in which activity can influence allocation before a learning event, we virally co-expressed the inhibitory and excitatory opsins eNpHR3.0 and ChR2(H134R) in the LA of mice (~10% of neurons) using a herpes simplex virus vector (HSV-NpACY). Transiently increasing the excitability of opsin-expressing neurons with blue light activation of ChR2 6h before auditory fear conditioning was sufficient to induce cause allocation to those neurons, as indicated by the ability to attenuate memory expression with red-light activation of NpHR. In contrast, memory could not be inhibited if the increase in activity occurred 24h prior to fear conditioning.
Increases in activity that drive memory allocation are also accompanied by inhibition of surrounding neurons, presumably through activation of parvalbumin+ interneurons. We hypothesized that this was a form of feedforward inhibition such that neurons with increased

activity inhibited their neighbors. To examine this possibility, we virally expressed NpACY fused to tetanus toxin light chain (NpACY-Tx) in the LA, which prevented neurotransmission from opsin-expressing cells without interfering with their ability to receive input. Optogenetically activating principal neurons expressing NpACY-Tx before fear conditioning was unable to induce allocation, evidenced by the inability to inhibit freezing during NpHR stimulation relative to mice expressing only NpACY. Furthermore, nuclear mRNA levels of the neuronal activity marker *Arc* revealed that blocking the output of excitable principal neurons increased the size of the memory trace by permitting the recruitment of neighbouring cells, similar to previous studies that inhibit LA interneurons after training. Our findings suggest that in the LA, local interactions between excitatory and inhibitory neurons can govern memory allocation well before learning, and that highly excitable principal neurons may suppress the activity of neighbouring cells through a disynaptic circuit mechanism to become the engram.

**Disclosures: J. Yu:** None. **A.J. Rashid:** None. **C. Yan:** None. **A. De Cristofaro:** None. **P.W. Frankland:** None. **S.A. Josselyn:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.06/UU9

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Optogenetic recovery of memories 'lost' to infantile amnesia

**Authors: *A. GUSKJOLEN**, S. A. JOSSELYN, P. W. FRANKLAND
Sick Kids Hosp., Toronto, ON, Canada

**Abstract:** Infantile amnesia refers to the inability of adults to remember episodic events from the earliest years of their lives. Previously, we showed that high rates of hippocampal neurogenesis during infancy contribute to this accelerated forgetting, likely by remodeling hippocampal circuits in which memories are embedded. Here, we tested whether this forgetting is due to a deficit in memory storage or retrieval. To do this, we trained infant mice in contextual fear conditioning and tested them 1-90 days later. Contextual fear memory was robust when tested 1 day after training. However, a dramatic decease in conditioned freezing occurred 15 days following training, and was close to floor levels by days 30-90, indicating that comprehensive forgetting had occurred. To test whether this forgetting was due to a failure of retrieval, we next tested whether environmental reminders could recover these lost memories. To do this, infant mice were trained as before, placed back into the same context 15-90 days later, and given a reminder shock. At all delays, the reminder shock induced freezing in the previously trained mice (but not age-matched naïve controls). This result suggests that the engram supporting this memory is not completely degraded and is recoverable with appropriate cuing. If this is the case,

then artificial activation of the engram should be sufficient to recover the memory 'lost' to infantile amnesia. To test this possibility, we trained infant mice in which we could indelibly tag populations of neurons that were active at the time of encoding with ChR2 (Arc-cre$^{ERT2}$ x ChR2). Reactivation of tagged neurons in the dorsal dentate gyrus (DDG) was sufficient in reinstating the memory 15, 30, and even 90 days following training. Memory retrieval is thought to engage neuronal populations in distributed networks extending far beyond the DDG. To evaluate whether neural activation of tagged DDG neurons 15-90 days post-training induced reactivation of tagged neurons elsewhere in the brain, we examined induction of the immediate early gene c-Fos following testing. We found that light stimulation of tagged DDG increased reactivation of tagged neurons in a variety of neural regions known to be important for memory retrieval (including the CA1 and CA3 subregions of the hippocampus, retrosplenial cortex, anterior cingulate cortex, and basolateral amygdala), suggesting that a brain-wide pattern completion like process was engaged. Together, these results suggest that infantile amnesia is due to a retrieval failure and that either environmental cuing or direct engram activation promote a pattern completion process that leads to successful recovery of memories lost from infancy.

**Disclosures: A. Guskjolen:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** HFSP LT000759/2014

CIHR FDN143227

**Title:** Towards the generation of an adult zebrafish digital brain atlas

**Authors: *J. W. KENNEY**[1], P. E. STEADMAN[2], S. A. JOSSELYN[3], P. W. FRANKLAND[4]
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**Abstract:** Adult zebrafish are an increasingly popular and important animal model in neuroscience research. As a genetically tractable vertebrate with a sophisticated behavioral repertoire and high genetic similarity to humans (70%), zebrafish are an ideal system for the study of neurobiology and behavior in both health and disease. However, although a comprehensive brain atlas for adult zebrafish was published over 20 years ago in book form, the field is lacking a digital brain atlas necessary for whole brain mapping studies. Here, we report

on our progress in creating such an atlas by combining tissue clearing techniques with light sheet microscopy, automated image registration, and manual parecellation. We anticipate that the generation of such an atlas will significantly increase the utility and sophistication of adult zebrafish as an animal model in neuroscience research.

**Disclosures: J.W. Kenney:** None. **P.E. Steadman:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSF Grant 1353137

NIH Grant MH105125

David C. Hodgson Endowment for Undergraduate Research Award

**Title:** Communication between retrosplenial cortex and auditory cortex is necessary for the expression of remotely-acquired fear to an auditory cue

**Authors: *M. Y. JIANG**, T. P. TODD, N. E. DEANGELI, D. J. BUCCI
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**Abstract:** Prior studies have shown that secondary sensory cortical areas are needed for the recall of remotely-acquired (28 days after training) but not recently-acquired (1 day after training) cue-specific fear memories. Similarly, our lab has recently discovered that the retrosplenial cortex (RSC) is also necessary for the recall of remote, but not recent tone-fear memories. RSC receives strong unimodal sensory input from various sensory modalities and is positioned as an interface between cortical sensory regions and a hippocampal/parahippocampal regions, leading us to propose that RSC may function as a ‘hub’ for the integration of sensory information in the service of recalling remotely-acquired memories. If so, we hypothesize that communication between RSC and regions of sensory cortex should be needed for recalling remote memories. To test this, male Long-Evans rats received 3 pairings of a tone and foot shock in a single training session. Twenty-eight days later, rats were randomly assigned to one of three groups. In the ‘asymmetric’ lesion group, the RSC and secondary auditory cortex (AC2) were fully disconnected by lesioning the RSC in one hemisphere and secondary auditory cortex (AC2) in the opposite hemisphere. The ‘symmetric’ lesion group received unilateral electrolytic lesions of RSC and AC2 in the same hemisphere, thus leaving communication in one hemisphere intact. Control rats received sham-lesions. After recovering from surgery for 2 weeks, all rats were re-

exposed to the training context and to the tone (in a different environment) to assess contextual and cue-specific fear memory, respectively. Compared to the control group, rats with asymmetric cortical lesion exhibited a severe impairment in freezing to the auditory cue, while rats with symmetric lesions exhibited an intermediate impairment. In contrast, rats in the two lesion groups exhibited comparable impairments in freezing to the context. Together, these results indicate that communication between RSC and AC2 is necessary for the retrieval of remote auditory fear memory, but not remote context fear memory. These findings have particular relevance for understanding the neural substrates of PTSD, in which individuals experience abnormally strong fear memories for events that happened in the distant past.

**Disclosures:** **M.Y. Jiang:** None. **T.P. Todd:** None. **N.E. DeAngeli:** None. **D.J. Bucci:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

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**Support:** NSF Grant 1353137

**Title:** Communication between retrosplenial cortex and prefrontal cortex is necessary for inhibitory learning and behavior

**Authors: *M. EDDY**, R. HUSZAR, D. J. BUCCI, PhD
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**Abstract:** The ability to modify behavior based on environmental information and feedback is critical for survival. Indeed, an essential aspect of adaptive behavior is to be able to recognize and use information about the current environmental setting, or *context*, to guide behavioral responding. In this way, contextual cues often indicate whether or not a particular response will result in a favorable outcome, and if not, that it should be inhibited. To date, a substantial amount of research has focused on the involvement of the prefrontal cortex (PFC) in response inhibition. At the same time, research from our laboratory and others has revealed that posterior cortical areas, such as retrosplenial cortex (RSC), are essential for encoding and retrieving contextual information. However, these two lines of research have proceeded relatively separately and it remains largely unknown if and how PFC and RSC interact to support the use of contextual information to guide behavior. Here we tested the hypothesis that contextual information provided to PFC from RSC is essential for effective behavioral inhibition. In Experiment 1, rats with RSC lesions were tested on an extradimensional set-shift task in which responding based on a previously learned rule must be inhibited and new rules applied, a process known to rely upon the PFC. Rats with RSC lesions were impaired at the shift portion of this task, but performed

similarly to sham-lesioned rats during the initial discrimination. In Experiment 2, we targeted and selectively inhibited neurons projecting from RSC to PFC during a test of operant extinction to further scrutinize the importance of contextual information provided by the RSC to the PFC. Rats were trained to lever press in one context (context A) and then extinguished in a different context (B). Testing occurred in extinction (no reward available) in both contexts, during which neurons in the PFC that receive projections from RSC were inhibited. Selective inhibition of this pathway resulted in increased responding (compared to controls) in both the acquisition (A) and extinction (B) contexts, indicating an inability to inhibit lever pressing. Taken together, these results suggest that projections from the RSC to PFC are critical for inhibitory control of behavior.

**Disclosures:** **M. Eddy:** None. **R. Huszar:** None. **D.J. Bucci:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

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**Topic:** H.01. Animal Cognition and Behavior

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**Title:** Damage to postrhinal cortex has no effect on the expression of remote cue-specific fear memory but does impair the renewal of conditioned fear

**Authors: *D. FOURNIER**[1], N. E. DEANGELI[2], D. J. BUCCI[3], T. P. TODD[2]
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**Abstract:** The postrhinal cortex (POR) is part a network of posterior cortical regions that provide the hippocampus with processed sensory information. Prior studies have demonstrated that POR is critically involved in hippocampal-dependent processes, such as contextual fear conditioning. Specifically, lesions of the POR carried out either prior to, or at various times after fear conditioning (e.g., 1, 28 or 100 days) impair the expression of fear to the training context. In contrast, pre-training lesions of POR do not affect the expression of fear to a discrete cue (e.g. a tone) that was paired with foot shock. However, it is currently unknown whether POR damage that occurs after training affects cue-specific fear memory. This is important to address because recent evidence indicates that over time, cue-specific memories can become dependent on polymodal cortical associations areas that are associated with the hippocampus. Furthermore, it is unknown if the POR is necessary for the extinction and/or renewal of cue-specific fear

memories. This is also a significant gap in the literature since renewal is not impacted by hippocampal damage in certain cases, suggesting that extinction and renewal of conditioned fear might also depend upon other regions such as the POR. To address these questions, rats received a single conditioning session in Context A, with three cue-shock pairings. Twenty-eight days later, rats received lesions of the POR. After recovering from surgery, rats were placed back in Context A (no shocks) to assess contextual fear memory, and the next day, the tone was presented 20 times in Context B (no shocks). Rats in the lesion group exhibited reduced contextual fear (consistent with prior studies) but intact fear to the tone. Rats then underwent three days of extinction training with 20 tones presentations in Context B each day. Following the last day of extinction training, renewal of extinguished fear was tested in Context A via 20 presentations of the tone. We found that POR lesions did not impact extinction training, but did result in lack of renewal of conditioned fear to the tone.

**Disclosures: D. Fournier:** None. **N.E. DeAngeli:** None. **D.J. Bucci:** None. **T.P. Todd:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

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**Title:** Retrosplenial cortex is required for the retrieval of remote fear memory for visual cues

**Authors: *D. J. BUCCI**, M. Y. JIANG, N. E. DEANGELI, T. P. TODD
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**Abstract:** A significant body of literature has demonstrated that damage to the retrosplenial cortex (RSC) impairs contextual and spatial learning in humans as well as laboratory animals. In contrast, memory for individual stimuli (cue-specific memory) appears to be largely intact following RSC lesions or temporary inactivation. In our own lab, for example, RSC damage that occurs either prior to, or 1 day after, auditory fear conditioning impairs the subsequent recall of contextual fear memory but not tone fear memory. However, a small but growing number of studies indicate that RSC may in fact have a role in cue-specific memory under certain circumstances. For instance, we recently found that manipulations of RSC at more remote times after training (28 days) impair both context and tone-specific fear memory. Based on this finding, and the known interconnectedness of RSC with a variety of unimodal cortical sensory regions, we posit that over time, cue-specific memories may become more dependent on RSC. If

so, we might expect that this function also applies to cues of sensory modalities other than audition. To test this, rats underwent fear conditioning in which a visual stimulus (a light) was paired with footshock during a single training session. Either 1 day (recent memory) or 28 days later (remote memory), rats received lesions of RSC and were allowed to recover before being re-exposed to the training chamber to test context fear memory, and to the light (in a different chamber) to test fear memory to the light. Control rats received sham-lesions. We found that RSC lesions impaired the expression of fear to the light when they took place 28 days after training, but not 1 day after training. In contrast, lesions at both time points impaired contextual fear memory. These findings replicate our prior results using an auditory stimulus, thus further supporting the notion that RSC has a selective, time-dependent role in expressing fear memory to specific cues. In contrast, the effects of RSC damage on context fear memories have repeatedly been shown to be independent of the training-to-lesion interval.

**Disclosures: D.J. Bucci:** None. **M.Y. Jiang:** None. **N.E. DeAngeli:** None. **T.P. Todd:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

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**Title:** Characteristic neocortical circuits encode different visual shape discriminations

**Authors: *A. I. GELLER**[1], G. ZHANG[1], H. ZHAO[1], N. COOK[1], M. JAN[1], E. CHOI[1], M. SVESTKA[1], R. G. COOK[2]
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**Abstract:** Synaptic plasticity and neural network and theories specify that the essential information for cognitive discriminations is encoded in different neuronal ensembles. But these ensembles are poorly characterized. One critical issue is if a specific discrimination is encoded in a characteristic ensemble among multiple individuals. In this study (Behav Brain Res In Press), we used a genetically-modified circuit that encodes essential information for a cognitive task to

show that characteristic ensembles encode specific visual shape discriminations.
For the model system, using a virus vector, we delivered a constitutively active protein kinase C into several hundred glutamatergic or GABAergic neurons in a multimodal associative area, postrhinal (POR) cortex, that has a critical role in visual object discrimination learning (J Neurosci 2005 *25* 8468-81). This intervention resulted in phosphorylation of specific PKC substrates that have important roles in synaptic plasticity. Further, activation-dependent neurotransmitter release was increased. Of note, this intervention supported enhanced the learning rate and accuracy for specific visual shape discriminations learned after gene transfer. The genetically-modified circuit encodes some of the essential information for performance (PNAS 2010 *107* 14478-83). Following gene transfer and learning image sets, we made neurochemical lesions that ablated the genetically modified circuit, ~21 % of POR cortex, centered on the gene transfer site. These lesions selectively reduced performance for discriminations learned after gene transfer.
During learning, neurons in the genetically-modified circuit exhibit increased activity, as shown by activity-dependent gene imaging. Quantifying these neurons showed that the essential circuit was small, ~500 neurons, and was sparse coded, with a coding density of ~3 %, consistent with neural network theory.
By analyzing the locations of the active neurons, we found that different image sets are encoded in characteristic and different ensembles of neurons (Behav Brain Res In Press). Specifically, there was a bilaminar pattern of active neurons. One layer of active neurons was near the surface of POR cortex, in layers 2, 3, and the superficial part of layer 4; and the second layer of active neurons was deeper, in the deeper part of layer 5 and in layer 6. Further, for one image set ([] vs. +) the superficial layer contained more active neurons than the deeper layer. But, for a second image set (/ vs. \), the two layers contained similar numbers of active neurons. Thus, different discriminations are encoded in characteristic and different neuronal ensembles.

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**Poster**

**522. Learning and Memory: Neural Circuits**

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**Topic:** H.01. Animal Cognition and Behavior

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NIMH MH081162

NINDS NS059312

**Title:** In search of an objective measure of working memory

**Authors: *B. CONKLIN**[1], W. HAHN[1], N. M. DOTSON[3], C. M. GRAY[4], S. L. BRESSLER[2]
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**Abstract:** Working memory (WM) is a cognitive system that contains internal representations of recent events for a pending action. Clinicians rely on subjective measurements of WM for diagnosis and treatment of memory disorders like Alzheimer's Disease and dementia with Lewy bodies. Our work shows that a signature of working memory may be derived from analysis of oscillatory neuronal population activity from monkeys and that this signature allows differentiation between healthy and impaired WM. First, we use supervised machine learning to identify sparse feature representations of local field potentials (LFPs) recorded from prefrontal and posterior parietal regions during the delay period of a delayed match-to-sample (DMS) task with both correct and incorrect performance by macaque monkeys. Then, these sets of feature representations serve as dictionaries for correct and incorrect WM neuronal population activity, respectively. The dictionaries are characterized by their spectral composition. Next, we develop a discrimination algorithm to predict whether novel trials contain correct or incorrect responses. The correct performance dictionary contains significantly different spectral components than the incorrect performance dictionary. We conclude that delay-period LFP activity during the DMS task allows for successful discrimination between correct and incorrect response classification, and that the monkey’s correct responses represent healthy WM and the incorrect responses represent impaired WM. Thus, our results establish that different spectral components characterize healthy and impaired WM, and that delay activity during a WM task can discriminate between healthy and impaired WM. The signature of WM will be tested in the human EEG in future studies of the same task.

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**Poster**

**522. Learning and Memory: Neural Circuits**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH NINDS RO1NS088661

**Title:** Neuromodulatory predictions: Comparison of forebrain cholinergic and midbrain dopaminergic responses during reinforcement learning

**Authors: *J. F. STURGILL**[1], S.-J. LI[2], B. HANGYA[3], A. KEPECS[2]
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**Abstract:** Basal forebrain (BF) cholinergic (ChAT) neurons project throughout cortex and, by modulating cortical plasticity, may support learning. Yet the principles governing ChAT neuron activation, and the precise relationships of cholinergic signals to learning and other neuromodulatory signals have remained obscure. Recent work from our lab revealed that ChAT neurons respond rapidly (~20ms) to reinforcers (reward, punishment) and are modulated by reinforcement expectation or surprise. A putative role in reinforcement prediction invites comparison to dopamine neurons for which a key conceptual advancement was that they compute reward prediction error (RPE): the difference between reward expectation (as informed by a predictive stimulus) and reward received. Here, we adopt an analogous behavioral and computational approach to understand the principles governing ChAT neuron activation. Do ChAT neurons respond only to reinforcers or also to outcome-predictive sensory cues? Are the outcome-related responses modulated by the degree of surprise, as for dopamine neurons? And computationally, do ChAT responses represent an unsigned counterpart to dopaminergic RPE? Using single and dual fiber photometry, we simultaneously monitored the responses of BF ChAT neurons and midbrain dopamine neurons in a cued probabilistic outcome task. As a reference point, we measured bulk GCaMP responses of dopaminergic neurons, which showed the canonical features of RPE, and confirmed that ChAT neurons respond to both reward and punishment. During learning we found that ChAT neurons rapidly acquire cue responses to predictive stimuli. We further demonstrated that outcome responses of ChAT neurons are diminished by reward expectation. Using dual fiber measurements in a reversal learning paradigm, we examined the fine-scale relationships between ChAT and dopamine neuron activity and observed a striking but partial correspondence between the two systems within and across learning trials. Our results demonstrate that BF ChAT neurons provide a cortical prediction error signal computationally distinct from but coordinated with dopaminergic RPE.

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and PAPIIT 204615

21-0159H

**Title:** MRI volumetric changes in brain areas during taste learning: Effects of long-term sugar consumption

**Authors: *M.-I. MIRANDA**[1], J. P. LERCH[2], N. MESA[3], D. A. VOUSDEN[3]
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**Abstract:** Recognition memory is the ability to assert the familiarity of things previously encountered; one of the most important survival skills that animals have developed through evolution is taste-recognition memory. Using taste memory model such as preference test and conditioned taste aversion (CTA), the neural pathways involved in learning have been well described by several electrophysiological and anatomical studies. Recently, evidence in rodents showed that long-term sugar consumption produces changes in the appetitive and aversive learning processes and suggests that, prolonged sugar intake, could trigger an escalating consumption of sweet taste due to changes in several brain areas involved during taste learning and reward responses. Mouse imaging studies show that learning alters the volume of specific brain regions. For example, environmental enrichment and spatial learning are associated with increases in hippocampal volume at a scale detectable with mouse MRI, providing an insight into anatomical changes and interactions between brain areas induced by long-term memory. However, volume changes related with taste learning and prolonged exposure of sweet taste, have not yet been described. Therefore, we used *in vivo* manganese-enhanced MRI (MEMRI), in healthy adult mice that undergo two weeks of voluntary sugar solution drinking, to map the macroscopic structure changes related with high familiar taste appetitive learning, as well as their correlation with the ability to achieve new taste aversive associations. MEMRI images were acquired 1 and 3 days before taste presentation (baseline), as well 1 and 2 weeks after mice were exposed to 10% sucrose solution or water as the only liquid available. Subsequently, to evaluate the latent inhibition of CTA induced by sucrose exposure, two more MEMRI were done, after CTA retrieval and one week later when aversive memory was completely extinguished. Automated image processing algorithms were used to detect volume changes associated with long term sugar consumption. The results showed volume changes in the brain areas directly related with taste memory formation, particularly insular cortex and amygdalar complex, and several significant interactions with reward pathway-related areas.

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NARSAD Young Investigator Grant

**Title:** Evaluation of neuronal activity patterns at the population level during contextual fear discrimination learning

**Authors: *A. CORCHES**, A. HIROTO, T. BAILEY, J. SPEIGEL, J. PASTORE, J. MAYER, E. KORZUS
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**Abstract:** Discriminatory fear learning involves fear conditioning, a form of classical Pavlovian conditioning which has become the best studied behavioral model for associative learning along with its underlying synaptic and circuit level plasticity. Fear behavior is differentially regulated by the prelimbic (PL) and infralimbic (IL) subdivisions of the mPFC via fear excitation and inhibition, respectively, which may be due to differential connectivity with amygdala. Current research investigates how the PFC is able to act through multiple pathways to exert both excitatory and inhibitory influences on fear responses under the central hypothesis that accuracy of fear memory is attained via extinction of fear responses to non-reinforced stimuli. Neuronal activity at a population level can be effectively studied in the brain using calcium imaging or Arc gene-based TetTag bi-transgenic mice, in which neuronal activities can be persistently labeled during a specific time window. We evaluate large-scale neuronal activity patterns in response to dangerous and safe contextual stimuli within relevant brain regions including the hippocampus, the mPFC and the amygdala during different phases of fear discrimination learning to uncover the neural mechanisms underlying ability to distinguish between danger and safety. Understanding how fear memories are encoded and kept resistant to confusion is clinically relevant because fear memory generalization is a hallmark of phobias, PTSD and generalized anxiety disorder.

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KIST institutional program 2E26860

**Title:** The thalamic reticular nucleus controls fear extinction

**Authors: *J.-H. LEE**[1], C.-F. V. LATCHOUMANE[1], J. PARK[1,2], J. KIM[3], K.-H. LEE[2], H.-S. SHIN[1]
[1]Ctr. for Cognition and Sociality, Inst. for Basic Sci. (IBS), Daejeon-City, Korea, Republic of; [2]Dept. of Bio and Brain Engin., Korea Advanced Inst. of Sci. and Technol. (KAIST), Daejeon, Korea, Republic of; [3]Ctr. for Functional Connectomics, Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

**Abstract:** The thalamic reticular nucleus (TRN), a shell of GABAergic neurons surrounding the thalamus, provides one of the most significant inhibitory inputs to the thalamus, thereby playing a pivotal role in sensory processing, attention control, and sleep modulation. Although previous anatomical data suggest a potential role of the TRN in emotional processing, this issue remains unexplored. Here, we show that a specific subregion of the TRN is critical in fear extinction. We conducted neural tracing experiments in mice and observed that the rostroventral part of the TRN (TRNrv) projected to the limbic thalamus, including the paraventricular nucleus of the thalamus (PVT), known to be important in fear regulation. By contrast, the neighboring rostrodorsal part of the TRN (TRNrd) projected to the centrolateral thalamus (CL). Our behavioral studies showed that optogenetic inhibition of TRNrv neurons suppressed fear extinction, whereas inhibition of TRNrd neurons did not affect fear extinction. Our *in vivo* recordings demonstrated an increased firing rate of TRNrv neurons during fear extinction learning, and boosting the firing rate led to enhanced fear extinction. Moreover, optogenetic inhibition of TRNrv terminals in the PVT resulted in the persistent elevation of fear. Our results reveal a previously unknown role of the TRN, control of emotional behavior, and a critical circuit for fear memory modulation.

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HHMI

**Title:** Long-term imaging of ensemble neural calcium dynamics in the perirhinal cortex of freely behaving mice learning context-stimulus associations

**Authors: *T. ROGERSON**[1], J. MAXEY[1], P. JERCOG[1], T. H. KIM[1], S. EISMANN[1], B. AHANONU[2], B. GREWE[1], J. LI[1], M. J. SCHNITZER[2]
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**Abstract:** The rodent perirhinal cortex has an established role in object recognition, but the role of perirhinal cortex in associative learning is less well explored. Electrical recordings in perirhinal cortex have identified neurons that represent objects [Burke et al., Hippocampus (2012) 22(10):2032-2044], but how such representations develop with learning and are influenced by contextual cues remains unknown. To study the role of the perirhinal cortex in associative learning, we used a miniature fluorescence microscope to record perirhinal ensemble neural calcium dynamics in freely behaving mice as they learned a task requiring mastery of a bi-conditional rule. This behavioral task involved two visuo-tactile stimuli that were independently presented in two different spatial contexts. In each context, only one of the two stimuli signaled the presence of a reward; thus, to receive rewards successfully in both contexts the mouse had to learn two different context-stimulus associations. With 8-10 days of training mice learned to perform this task well, even when rapidly alternating between the two contexts. As the mice performed the task, the dynamics of perirhinal neural ensembles encoded task-relevant variables such as stimuli and context, and these representations remained distinct and stable throughout the learning process. By varying stimulus locations within and across the two contexts, we found that stimulus representations in the perirhinal cortex were invariant to location and reward contingency, unlike what we had found previously in hippocampus, where neural coding was more dynamic. Together, the invariant coding in perirhinal cortex and the more dynamic coding in hippocampus may jointly support an animal's ability to recognize stimuli reliably across different contexts while responding in a context-specific manner.

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**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.19/UU22

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant NS094009

**Title:** Changes in membrane properties of neurons in the deep cerebellar nuclei as a result of eyeblink conditioning in adult rats

**Authors: D. WANG**, L. B. BURHANS, D. E. O'DELL, C. A. SMITH-BELL, *B. G. SCHREURS
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**Abstract:** Previous studies have shown changes in membrane properties of neurons in rat deep cerebellar nuclei (DCN) as a function of development, but due to technical difficulties in obtaining viable DCN slices from adult animals, it remains unclear whether there are learning-related alterations in membrane properties of DCN neurons in adult rats. We performed whole-cell patch clamp recordings on DCN neurons in rats aged P25-26 given delay eyeblink conditioning or unpaired stimulus presentations. One day after electromyography electrode implantation, adult rats received either four sessions of delay eyeblink conditioning or four sessions of unpaired stimulus presentations with a tone as conditioned stimulus and a shock as unconditioned stimulus. Compared to rats given unpaired stimuli, rats given eyeblink conditioning showed a rapid increase in conditioned responses across sessions. Whole cell recordings from the rats given eyeblink conditioning revealed significant changes in membrane properties of DCN neurons including a reduction in afterhyperpolarization amplitude (-10.23 ± 1.00 vs -13.71 ± 1.27 mV, $p<0.05$) and an increase in input resistance (118.59 ± 13.14 vs 85.88 ± 13.43 MΩ, $p<0.05$) - indexes of membrane excitability that have been shown to be important for eyeblink conditioning in hippocampus and prefrontal cortex. This is the first report of learning-related changes in membrane properties of adult DCN neurons which may underlie acquisition of eyeblink conditioning.

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**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.20/UU23

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Distinguished Young Scholars of China(31525010)

**Title:** Improving working memroy performance by suppressing lateral orbitofronto-striatal pathway

**Authors: *C. QI**[1,2], R. Q. HOU[1], Z. Q. CHEN[1], H. M. FAN[1], C. Y. LI[1]
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**Abstract:** Working memory (WM) is the ability of actively maintaining and manipulating information in the brain and important for cognitive behaviors (Baddeley 2012). Many previous studies have shown that persistent neural activity of many brain regions are important for WM (Fuster 1997, Pasternak and Greenlee 2005, Jonides, Lewis et al. 2008, D'Esposito and Postle 2015, Eriksson, Vogel et al. 2015, Christophel, Klink et al. 2017). However, how to improve WM is less clear. In the current study, head-fixed mice were trained to perform an olfactory delayed paired association (DPAL) task, in which sensory information was required to be maintained during a delay period of 5-10 seconds.. The activity of lateral orbitofrontal cortex (LOFC) was optogenetically suppressed during the delay period in blind design. Surprisingly, the performance of mice was improved during the learning phase. The phenomenon was consistently observed with different parameters, including varying delay duration or using ibotanic-acid lesion to suppress LOFC activity. The improvement was regionally specific, because suppressing ventral or medial part of orbitofrontal cortex did not modulate performance. The effect was also temporally specific, because suppressing LOFC during the decision making period had no effect to performance. To determine downstream pathways of LOFC in improving WM performance, we expressed optogenetic virus into LOFC and used light to separately suppress the activity of axonal terminals in different downstream brain areas, including dorso-medial caudate/putamen (dmCP) of striatum, ventral tegmental area (VTA), perirhinal cortex, and secondary motor cortex. Among the four regions, only suppression the activity of LOFC-dmCP projection improved WM performance. To determine the neural correlates of LOFC in the WM task, we extracellularly recorded single-neuron activity by tetrode. We found that the neuronal activity in LOFC clearly encoded the odor identity during the delay period, especially during the early delay period. Therefore the presence of neural correlates in LOFC negatively regulated WM performance. In summary, the results discovered a surprising improvement in WM performance by optogenetic suppression of LOFC-dmCP pathway. Baddeley, A. (2012). Annu Rev Psychol **63**: 1-29.Christophel, T. B., et al. (2017). Trends Cogn Sci **21**(2): 111-124.D'Esposito, M. and B.

R. Postle (2015). Annu Rev Psychol **66**: 115-142.Eriksson, J., et al. (2015). Neuron **88**(1): 33-46.Fuster, J. M. (1997).Jonides, J., et al. (2008). Annu Rev Psychol **59**: 193-224.Pasternak, T. and M. W. Greenlee (2005). Nat Rev Neurosci **6**(2): 97-107.

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**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.21/UU24

**Topic:** H.01. Animal Cognition and Behavior

**Support:** UNSW Gold Star 2016

**Title:** The effect of a high sugar diet on context-dependent memory and neuroinflammation in rats

**Authors: *K. N. ABBOTT**[1], M. J. MORRIS[2], R. F. WESTBROOK[1]
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**Abstract:** The hippocampus binds the individual elements of a context (e.g. a room) into a unique integrated representation that facilitates subsequent discrimination of that context from other similar contexts and, thus, displays of context-appropriate behaviour. Research in rodents demonstrates that excessive sugar consumption impairs hippocampal-dependent spatial memory, and that this deficit may be mediated by diet-induced neuroinflammation. It remains unknown however whether these deficits in spatial memory extend to the formation of unified context representations and retrieval of context-dependent memory. In this research, we used a rodent model to assess the effect of a high sugar diet on context-dependent memory and neuroinflammation. Rats were provided ad libitum access to chow and water (control diet; CD) or chow, water, and 10% (w/v) sucrose solution (high sugar diet; HSD). Spatial memory was assessed after four weeks diet using an object-and-place recognition memory test. After six weeks, rats were assessed for their ability to discriminate a context where they had received a mild aversive foot shock from a similar yet distinct context. After eight weeks, rats were sacrificed and neuroinflammation within the hippocampus was assessed using an Interleukin-1-beta (IL-1β) Enzyme Linked Immunosorbent Assay. Analysis revealed that rats consuming a HSD had impaired hippocampal-dependent spatial memory and context-dependent memory, as well as increased levels of the neuroinflammatory marker IL-1β. There were no correlations between deficits in spatial memory, context-dependent memory, and level of neuroinflammation, irrespective of diet condition. This research provides reasonable evidence that high sugar consumption negatively influences the ability of the hippocampus to form context

representations, and that this can lead to displays of context-inappropriate behaviour. Further research is required before neuroinflammation can be excluded as a mediator of these diet-induced cognitive deficits.

**Disclosures: K.N. Abbott:** None. **M.J. Morris:** None. **R.F. Westbrook:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.22/UU25

**Topic:** H.01. Animal Cognition and Behavior

**Support:** PhD fellowship: SFRH/BD/97442/2013

**Title:** Neural mechanisms of observational conditioning in zebrafish

**Authors: *J. PINHO**[1,2], P. LAL[3], K. KAWAKAMI[3], R. OLIVEIRA[2,1,4]
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**Abstract:** Group living animals can use public information when making decisions about the presence of threat in the environment. Social cues from conspecifics can be used not only to trigger a response but also as unconditioned stimulus (US) that can be paired with other cues in the environment (that will become conditioned stimuli, CS) in order to predict the presence of threat in the environment through associative learning (observational conditioning). The evolution of a specialized neural module to process social information has been the focus of much debated in comparative cognition literature. In this study we tested the occurrence of observational conditioning in zebrafish, and characterized its neuromolecular mechanisms. We found that chemical (alarm cue) but not visual (sight of conspecifics freezing) was effective as a US in the observational conditioning task. Next, we characterized the pattern of brain activation associated with olfactory observational conditioning using the expression of an immediate early gene (c-fos) as a marker of neuronal activity. Differential activation patterns were observed between learners and non-learners in olfactory bulb and dorsal medial telencephalon (Dm, teleost homologue of the basolateral amygdala in mammals). We created a transgenic zebrafish line that expressed the yeast Gal4 transcription factor in a specific neuronal population in Dm, and used it for the selective inactivation of Dm (by expressing a neurotoxin gene via the Gal4-UAS system). Then we tested the involvement of this brain region in observational learning (i.e. when a social US is used), and found that inactivation of the neuronal population impaired fear conditioning using the alarm cue as US.We showed that the same neuronal population is essential for fear conditioning using an electrical shock as US (Lal et al. submitted). Thus, our results support the

existence of a common neuronal population that mediates both observational and non-social fear conditioning.

**Disclosures:** **J. Pinho:** None. **P. Lal:** None. **K. Kawakami:** None. **R. Oliveira:** None.

**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.23/UU26

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Circuit mechanism of long term memory consolidation in *Drosophila*

**Authors: *U. DAG**, J. LE, Z. LEI, A. WONG, K. KELEMAN
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**Abstract:** *Drosophila melanogaster*, fruit flies, can associate either aversive or rewarding stimuli with odors to form aversive or appetitive olfactory memories, respectively. In addition to this simple form of associative learning, flies are also able to associate their behavior with its outcome. In courtship conditioning paradigm, *Drosophila* males learn to suppress their courtship towards either receptive virgin or unreceptive mated females after being persistently rejected by unreceptive females. Previously, we have shown that activity of dopaminergic aSP13 neurons that innervate the tip of the mushroom body gamma neurons, is required and sufficient for acquisition of the short-term courtship memory. More recently, we determined that activity of the same aSP13 neurons, after memory acquisition, is also sufficient and necessary for long-term courtship memory consolidation. To investigate the mechanisms underlying consolidation of this memory we examined the role of sleep in this process. We have established that sleep is both necessary and sufficient for memory consolidation in a manner similar to that of aSP13 neurons. More specifically, we identified neurons in a brain region implicated in homeostatic control of sleep, to be involved.

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**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.24/UU27

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIDA-IRP

NHMRC Australia

**Title:** An unlikely circuit for cue-reward learning

**Authors: *M. SHARPE**[1,2,3], N. J. MARCHANT[1,4], L. R. WHITAKER[1], C. T. RICHIE[1], Y. J. ZHANG[1,5], E. J. CAMPBELL[1], P. P. KOIVULA[1], J. C. NECARSULMER[1], C. MEJIAS-APONTE[1], M. MORALES[1], J. PICKEL[6], J. C. SMITH[7], Y. NIV[2], Y. SHAHAM[1], B. K. HARVEY[1], G. SCHOENBAUM[1,8,9]
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**Abstract:** Current theories of functioning in lateral hypothalamus (LH) restrict this region to promoting the innate drive to feed. This has been supported by evidence that LH stimulation promotes an increase in food consumption, recently demonstrated by stimulation of LH GABA cells alone. But this increase in feeding could reflect a more complex learning process. We are not born with a drive to approach particular foods; we have to learn that the sight and smell of such foods are associated with the rewarding aspects of their consumption for them to motivate future behavior. Using a novel GAD-Cre rat, we took advantage of the temporal specificity of optogenetics to dissociate a role for LH GABA in learning about food associates from a more traditional role in promoting feeding. In a Pavlovian conditioning procedure, we first showed that inhibition of LH GABA cells during cue presentation and not during reward delivery impaired the ability of rats to use the cue to predict future reward. Secondly, we showed that inhibition of LH GABA cells after normal learning had taken place reduced responding to the reward-predictive cue, suggesting LH is a site involved in the development and expression of cue-reward associations. We next examined how this cue-elicited expectation may be utilized at the circuit level. Here, we demonstrated that inhibition of LH GABA terminals in the ventral tegmental area (VTA) during cue presentation augmented learning. This is consistent with the notion that LH GABA sends cue-elicited expectations to VTA to modulate prediction errors, where depriving VTA of this signal resulted in persistent errors, driving greater learning about the antecedent cue. Finally, inactivation of VTA dopamine projections to LH during reward delivery also impaired learning, suggesting activity from VTA DA during reward is relayed back to LH to update cue-elicited expectations. These data demonstrate that the LH GABA- VTA circuit is critical for learning to use environmental stimuli to predict future rewards.

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**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.25/UU28

**Topic:** H.01. Animal Cognition and Behavior

**Title:** The ventral-striatum's role in learning from gains and losses

**Authors: *C. TASWELL**[1], V. D. COSTA[2], R. VICARIO FELICIANO[4], K. ROTHENHOEFER[5], B. B. AVERBECK[3]
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**Abstract:** Much of the literature on reinforcement learning (RL) suggests that the ventral striatum (VS) is crucial to the learning process. However, recent evidence suggests that this is not the case, and that the VS may have a more specific role in RL than previously thought. To assess the role of the VS in RL, we tested rhesus macaques with VS lesions on deterministic and stochastic two-arm bandit learning tasks. Typically, RL studies assessing the VS focus on appetitive learning treating lack of reward as aversive. Without studying both the appetitive and aversive side of RL one cannot assess what role the VS plays in aversive learning. To account for this, we conditioned tokens as reinforcers in a task where animals could both gain and lose tokens. This allowed us to assess learning from gains and losses. We ran three experiments; two used deterministic reinforcement and one used stochastic reinforcement. In each experiment there were three different types of conditions, gain gain (gg), gain loss (gl), and loss loss (ll). In the first deterministic experiment, for each new block of trials we introduced four novel images, where each image led to a different outcome when chosen (+2, +1,-1,-2). On each trial, monkeys were presented with a pair of images differing in value (six possible conditions). In this experiment, monkeys with VS lesions showed no significant behavioral deficits in any of the conditions relative to matched controls. The second experiment was the same as the first, except we added a cue with a value of 0 to the set (+2, +1, 0, -1, -2). This resulted in ten conditions. In this experiment, monkeys with VS lesions showed significant behavioral deficits in the gg condition (+2 vs +1), only. The final experiment was just like the first except it was under a stochastic reward schedule such that 75% of the time the outcome was the value of the cue, and 25% of the time the outcome was 0. In this experiment, monkeys with VS lesions again showed significant behavioral deficits only in the gg condition. Across the three experiments, no deficits were observed when choosing between a gain and a loss stimulus. Thus, the VS does not play a

general role in all forms of reinforcement learning, but plays a specific role in learning to select between rewarded outcomes.

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**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.26/UU29

**Topic:** H.01. Animal Cognition and Behavior

**Support:** National Research Foundation of Korea Grant 2015M3C7A1031395

**Title:** Medial prefrontal cortex lesions increase vulnerability to uncontrollable stress, resulting in cognitive impairments

**Authors: *J.-C. PARK**, D.-H. CHOI, J.-S. HAN
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**Abstract:** Exposure to uncontrollable stress may lead to cognitive impairments observed in post-traumatic stress disorder (PTSD) by affecting hippocampal functions. In recent years, it has been reported that medial prefrontal cortex (mPFC) plays an important role in the development of PTSD pathophysiology. However, it is unknown whether dysfunction of mPFC might influence cognitive status of the animals experiencing an uncontrollable stress. Therefore, the present experiment was conducted to examine whether mPFC lesions affect susceptibility to uncontrollable stress-induced memory impairments. After lesion surgery, rats were subjected to either 20-min restraint + 20 tail shock (20-min stress), which is ineffective in inducing memory impairments, or 60-min restraint + 60 tail shock (60-min stress) resulting in memory impairment. Cognitive status of these stressed rats was examined using novel object recognition task. Regardless of the mPFC lesion, rats that received 60-min stress exhibited impairments in object recognition memory compared with unstressed rats. Sham- operated rats with 20-min stress showed intact recognition memory, however, 20-min stress reliably led to impairments of recognition memory in rats with mPFC lesion. Next, the activity of the amygdala, measured by the expression of the c-fos protein, was analyzed 60 min after 20-min stress treatment. Compared to unstressed rats, the number of cells expressing c-fos was increased in both sham operated and lesioned rats. However, the increment of c-fos positive cells in mPFC lesioned rats was significantly higher than that in sham operated rats, indicating that mPFC lesion could predispose amygdala to hyperactivity in the stressful circumstance. These findings suggest that absence of mPFC, a loss of the ability to regulate the amygdala activity, increase vulnerability to traumatic stress effect on hippocampus and contribute to the development of behavioral phenotypes

associated with PTSD. Supported by the National Research Foundation of Korea grants 2015M3C7A1031395 to J.S.H.

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**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.27/UU30

**Topic:** H.01. Animal Cognition and Behavior

**Support:** DGAPA-PAPIIT IN204615

CONACyT 252379

**Title:** Effects of long term sugar or high fructose corn syrup (HFCS-55) consumption withdrawal on anxiety and corticosterone levels: Correlation with glutamate realase in the insular cortex during new aversive learning

**Authors: *D. BADILLO JUAREZ**, M. I. MIRANDA
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**Abstract:** Taste recognition memory is a crucial ability to associate taste-related properties with the consequences of food ingestion; therefore, the consumption of palatable caloric food has a significant impact on learned habits and preferences. The withdrawal of sugar after several weeks of intermittent feeding schedule in rodents induce significant behavior changes associated with increases in anxiety and stress hormones, and with changes in some neurotransmitters in overlapping brain circuitry that regulates food processing, as well as learning and memory; suggesting that reinforcers, such as sugars, stimulate similar neural systems. In this regard, the insular cortex has a crucial role during taste memory formation and food integration consequenses; particularly, glutamatergic activity is involved in signaling aversive visceral information during conditioned taste aversion (CTA). Furthermore, corticosterone (CORT) levels play an important role during taste aversive memory consolidation and the expression of anxiety behaviors. Thus the goal of this research was to evaluate in rats, the effects of long-term (21 days) permanent or intermittent sugar (10%) or HFCS-55 (8%) consumption, and their withdrawal, on preference taste and CTA, as well as on CORT plasma levels and anxiety-like behaviors, by means of elevated plus maze (EPM). Furthermore, we evaluated glutamate activity in the IC during new aversive learning (CTA) with the same sweetener. The results showed that consumption schedules induced significant differences in taste preference and CTA, but neither sugar nor HFCS-55 schedules, nor their withdrawal induced any change in EPM parameters or CORT levels. Microdialysis results in control groups revealed similar release of glutamate in the

IC induced by a visceral malaise agent (LiCl) during CTA. The results suggest that changes in taste memory after withdrawal of sugar or HFCS-55 permanent or intermittent long-term consumption are not related with anxiety behaviors or changes in stress hormone levels.Acknowledgments: Technical assistants Gabriela Vera and Alejandro Rangel-Hernández

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**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.28/UU31

**Topic:** H.01. Animal Cognition and Behavior

**Support:** ONR MURI N00014-16-1-2832

NIBIB R01EB022864

NIMH R01MH112169

NIMH R37MH087027

**Title:** Memory of what happened when as a compressed timeline in monkey lPFC

**Authors: *Z. TIGANJ**[1], J. A. CROMER[2], J. E. ROY[2], E. K. MILLER[2], M. W. HOWARD[1]
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**Abstract:** Cognitive theories suggest that working memory maintains not only the identity of recently-presented stimuli but also a sense of the elapsed time since the stimuli presentation. Previous studies of the neural underpinnings of working memory have focused on sustained firing, which can account for maintenance of the stimulus identity, but not for representation of the elapsed time. We analyzed single-unit recordings from the macaque lateral prefrontal cortex (lPFC) during performance of a delayed-match-to-category task. The sample stimulus triggered a consistent sequence of neurons, each neuron in the sequence firing during a circumscribed period of time. The sequences initiated by different sample stimuli were distinct but overlapping, with the degree of overlap reflecting the visual similarity of the stimuli that caused the sequences. These sequences of neurons encoded both stimulus identity and the elapsed time. The temporal code became less precise as the sample stimulus receded into the past. These findings suggest that working memory is maintained as a compressed timeline, consistent with longstanding cognitive theories of human memory. We describe also a neuro-cognitive computational model,

providing a neural mechanism that could give rise to the observed conjunctive coding over the log-compressed time.

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**Poster**

**522. Learning and Memory: Neural Circuits**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 522.29/UU32

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Distinct patterns of neural co-ordination support the binding of multi-modal memories across multiple brain circuits

**Authors: *A. J. MORLEY**[1], D. DUPRET[2]
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**Abstract:** In order for a memory to be useful it must be bound across multiple modalities. Here we recorded from multiple memory-associated regions in freely-behaving mice while they performed a task that requires the binding of auditory, valence and contextual/visual information. We show that, in this task, recall is accompanied by distinct short-term modes of co-ordination between these regions. These modes of co-ordination were identified from patterns found in the spike-train cross-correlations and are better predictors of both trial-identity and behaviour than the firing rate of the neurons alone. We thus hypothesize that they reflect efficient information routing across this memory-associated circuit and so support a rapid behavioural response.

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**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.01/UU33

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant R01 MH103325

**Title:** Hippocampal area CA3 is necessary for ripples and place field responses

**Authors: *H. DAVOUDI**[1,2,3,4], D. J. FOSTER[1,2,4]
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**Abstract:** The hippocampus has a critical role in the formation of new memories. The local field potential in hippocampal area CA1 exhibits high frequency (100- 250 Hz) events known as sharp-wave ripples (SWRs) which occur during both slow-wave sleep and awake rest. During exploration, CA1 pyramidal cells, which receive excitatory inputs from entorhinal cortex and hippocampal area CA3, show location-specific activity known as place fields. Previous studies have suggested that direct entorhinal input to CA1 is sufficient for the expression of ripples and ripple-asociated spiking in CA1 during rest, and for place field responses in CA1 during running. However, these studies used chronic manipulations allowing the possibility of compensatory mechanisms. Here we used an acute strategy, combining optogenetics and multi-tetrode recording, to suppress CA3 input to CA1. An AAV5 was delivered stereotaxically to CA3a and b, to drive subsequent expression of the light-sensitive proton pump eArchT3.0 in CA3 terminals onto CA1 cells. Drives consisting of 40 adjustable tetrodes and 2 adjustable optical fibers were targeted bilaterally to the pyramidal cell layer and stratum radiatum, respectively. Although the viral injection technique allowed for the possibility of uptake by nearby CA2 cells, the targeting of light to the stratum radiatum likely avoided suppression of CA2 inputs. Suppression of CA3 input revealed a severe reduction in CA1 ripples and ripple-associated unit activity. Further, in the absence of CA3 input, CA1 place field responses during running were greatly reduced with many cells ceasing to fire altogether. By contrast, hippocampal theta rhythm was enhanced during exploration, while theta phase precession remained intact. These findings shed light on the distinct contributions of different circuits to hippocampal information processing.

**Disclosures: H. Davoudi:** None. **D.J. Foster:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.02/UU34

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Effects of early experience on spatial representation of large-scale environments in the bat hippocampus

**Authors: S. R. MAIMON**, T. ELIAV, L. LAS, *N. ULANOVSKY
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**Abstract:** The proper function of brain circuits depends both on processes that require normal experience, and on processes which are independent of experience. The long-term effects of altered sensory experience on the brain have been extensively studied, but very little is known about the long-term physiological effects of abstract, cognitive experiences. The hippocampus offers an excellent substrate for addressing this question, because this high-level brain region is very far removed from the sensory periphery, and it contains abstract representations of space - yet, despite their abstractness, these spatial codes are amenable to detailed quantification. A number of studies have examined the normal development of spatial representations in the hippocampal formation of rat pups, during ontogeny; however, it is unknown how alterations in early experience affect spatial representation in the adult hippocampus - and in particular, the representation of naturalistic environments. We are addressing this question by investigating adult spatial representation of a very large environment in the hippocampus of laboratory-born bats, which were never exposed to large-scale environments (larger than a few meters) - and compare it to wild-born adult bats, which were exposed to very large spatial scales when they were flying outdoors. The main difference between these two groups of bats is in a very abstract parameter - the spatial scale of the environment that they experienced - whereas the sensory and motor experiences are normal for both groups of bats. We are using a miniature wireless electrophysiology system to record place cells in hippocampal area CA1 of laboratory-born bats that are flying in a very long 200-m tunnel, in comparison to wild-caught adult bats performing the same task in the same tunnel. Here we will present preliminary neuronal recordings that aim to elucidate how hippocampal representations are shaped by abstract features of early experience.

**Disclosures: S.R. Maimon:** None. **T. Eliav:** None. **L. Las:** None. **N. Ulanovsky:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.03/UU35

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Gating and scaling of the head-direction signal by angular velocity

**Authors: *A. FINKELSTEIN**[1,2], H. ROUAULT[1], S. ROMANI[1], N. ULANOVSKY[2]
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**Abstract:** Orientation in space requires a sense of direction that is thought to rely on head-direction cells - neurons that respond when the animal's head is facing a particular direction in space, analogously to a compass. A critical requirement for network models of head-direction cells is the ability to accurately track the head-direction at different turning velocities. Here we

recorded the neural activity in the dorsal presubiculum of Egyptian fruit bats, and found that contrary to the common view, head-direction tuning was strongly affected by angular velocity. First, the majority of recorded cells exhibited *gating* of head-direction tuning by angular velocity - whereby sharp head-direction tuning emerged at some angular velocities, but was completely absent at other velocities. Second, we also found a graded *scaling* of directional firing as function of turning velocities, i.e. a change in tuning-depth - with more neurons having a larger response at fast angular velocities. The scaling phenomenon was primarily manifested by a *redistribution* of spikes between the preferred and null directions of the neuron - such that the tuning-depth has changed dramatically but the total spike-count did not change as function of angular velocity. We further show that classical 'ring models' of head-direction tuning cannot explain these heterogeneous modulation properties of head-direction cells as function of angular velocity. We propose an alternative recurrent network model for head-direction cells, which comprises populations of neurons with heterogeneous cell-intrinsic properties. In this model, neurons with linear current-to-activity transfer functions exhibit tuning scaling by a redistribution of spikes, whereas neurons with sharper non-linearities scale by changes in the overall spike-count. We speculate that the presence of heterogeneities may improve the responsiveness of the head-direction system to sensory-based corrective signals.

**Disclosures: A. Finkelstein:** None. **H. Rouault:** None. **S. Romani:** None. **N. Ulanovsky:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.04/UU36

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Representation of 3D space in the entorhinal cortex of flying bats

**Authors: *G. GINOSAR**, A. FINKELSTEIN, L. LAS, N. ULANOVSKY
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**Abstract:** Grid cells exhibit spatially-periodic firing fields, and are thought to be important for navigation. When recorded in animals moving on a 2D plane, these cells fire when the animal passes through the vertices of a hexagonal grid spanning the 2D environment. Despite extensive research on 2D grid cells, there is an ongoing debate regarding the function of these fascinating neurons - namely, whether they encode the position of the animal or the distance it travelled. Moreover, many animals navigate through 3D space, but no studies to date have attempted to characterize the 3D volumetric firing of grid cells. Here, we conducted experiments in flying bats to elucidate the grid code in 3D. We trained Egyptian fruit bats (Rousettus aegyptiacus) to fly in a large flight room, while we wirelessly recorded single-neuron activity in medial entorhinal

cortex (MEC). Our results revealed structured firing in the 3D firing-rate maps, with multiple firing-fields. The spacing between firing-fields was more variable than in perfect synthetic 3D lattices (such as FCC or HCP sphere-packing grids), but was substantially less variable than for randomly-distributed fields - namely, 3D grid-cells seem to exhibit a fixed distance scale, without forming a global lattice. We also found a number of other spatial cell types in the MEC, including 3D border cells and 3D head-direction cells. Interestingly, we also found a subset of MEC neurons that tended to fire around balls on which the bat landed or took off. These neurons fired either as the bat took off or as the bat landed, but not in both cases; some of these cells showed even larger specificity and fired near a particular ball, but did not fire near other balls. Taken together, these data suggest a rich 3D spatial representation in the MEC of flying bats - including coding of 3D space by grid cells, coding of 3D geometry by border cells, as well as an object-related coding in the MEC.

**Disclosures: G. Ginosar:** None. **A. Finkelstein:** None. **L. Las:** None. **N. Ulanovsky:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.05/UU37

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Israeli Ministry of Absorbtion Grant

**Title:** Social place cells in the bat hippocampus

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**Abstract:** Social animals need to know the spatial position of conspecifics, both because it is important for them to know the locations of socially-dominant animals, and for purposes of group navigation. However, nothing is known about how the location of other animals is represented in the brain. Here, we addressed this question by studying bats - highly-social mammals that excel in observational-learning and are also outstanding navigators. We designed an observational-learning task for Egyptian fruit bats (*Rousettus aegyptiacus*), where animals were trained in pairs: In each trial, one bat (‘observer’) had to observe and remember the flight-trajectory of the other bat (‘demonstrator’). After a short delay, the observer had to imitate the demonstrator and fly along the same flight-trajectory to receive a reward - which required the observer to pay close attention to the demonstrator’s position. We recorded neurons in hippocampal area CA1 of the observer bat during this task, using a tetrode-microdrive and a miniaturized wireless electrophysiology system that allowed recording of individual neurons in freely behaving bats. A total of ~350 neurons were recorded in 5 bats. To control for the known

spatial properties of hippocampal place-cells, we did two things: first, the observer hung at a fixed position while it was observing ('space-clamp'); and second, we used a nine-axis motion sensor on the observer to exclude neural activity due to head-movements. We found CA1 neurons in the observer's hippocampus that represented the position of the demonstrator bat. About half of these cells represented the bat's own position (place cells) as well, but the other half did not. Further, the spatial representation of the demonstrator bat was unaffected by removal of spikes during sharp-wave-ripples - which have been linked to spatial 'preplay' and trajectory planning - and hence it cannot reflect spatial planning by the observer bat. Finally, we also found neurons in CA1 that represented the position of inanimate moving objects; this representation was different from the representation of the conspecific bat. Taken together, these data indicate a possible role for the hippocampus in social-spatial cognition.

**Disclosures: D. Omer:** None. **S.R. Maimon:** None. **L. Las:** None. **N. Ulanovsky:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.06/UU38

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Representation of large-scale spaces in the hippocampus of flying bats

**Authors: *T. ELIAV**, L. LAS, N. ULANOVSKY
Weizmann Inst. of Sci., Rehovot, Israel

**Abstract:** Most animals navigate daily over distances spanning from hundreds of meters to many kilometers. However, for the last forty years, hippocampal electrophysiological research has typically focused on spatial representations in small laboratory environments. Nothing is known about hippocampal neural codes for large spatial scales - in environments spanning hundreds of meters or kilometers - the scales of natural navigation of rodents, bats and other mammals. Here we aimed to address this fundamental question for the first time, by developing a unique recording setup that includes a large-scale ethologically relevant environment. We are using the Egyptian fruit bat as our animal model, because bats are excellent navigators over large natural scales, and because bats were shown to have rodent-like hippocampal spatial representations in small laboratory environments. So far, we took the following steps: First, we developed an on-board wireless neural-logging system, which allows recording single-units over unlimited distances. Second, we built a 200-m long tunnel where bats can fly freely. Third, to track the bat's position we utilized an RF localization device that measures distances to a ground-based antenna-array - yielding a spatial accuracy of ~10-cm, much better than GPS. Behavioral experiments showed that bats fly volitionally back-and-forth along the tunnel - more than 100 laps per session (>20-km total flight distance). Preliminary recordings of CA1 neurons

in the 200-m tunnel showed the following: (i) Individual hippocampal CA1 cells exhibited many fields per neuron. (ii) We found very large fields in dorsal CA1 - up to 20-30 meters. (iii) A given neuron could exhibit multiscale spatial coding - with different place-fields of the same neuron having very different sizes, ranging from 1 m to 20-30 m. (iv) Some of the firing properties, such as directionality and field-asymmetry, were similar to findings in small-scale environments in the laboratory. Taken together, most of the firing properties of CA1 neurons in this large-scale environment suggested a representation that is very different from findings reported so far in the laboratory - in any species.

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**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.07/UU39

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Janssen Pharmaceutical Companies of Johnson & Johnson

**Title:** Place cell ensemble function in a mouse model of chronic stress

**Authors: *T. INDERSMITTEN**[1], M. SCHACHTER[2], R. WYATT[1], N. WELTY[1], S. YOUNG[1], S. CAMPBELL[1], S. OTTE[2], J. NASSI[2], P. BONAVENTURE[1]
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**Abstract:** Chronic stress can lead to clinical depression, yet little is known about the underlying neuronal circuit dysfunctions in this complex mental disorder. The hippocampus, a structure essential for spatial navigation and memory, undergoes anatomical and functional changes during chronic stress. Here we utilized *in vivo* miniature fluorescence microscopy to examine place cell properties in the hippocampus and investigated how chronic stress perturbs hippocampal function. We implanted transgenic mice expressing the genetically encoded calcium indicator GCaMP6f in CA1 pyramidal neurons with microendoscope GRIN lenses and operant conditioned them to run on a linear track. To model physiological conditions of chronic stress, these mice were chronically administered with either 400 µg/ml of hydrocortisone, 10 mg/kg of the selective serotonin reuptake inhibitor Citalopram, or both. Hippocampal ensemble calcium event activity was recorded with nVista miniature microscopes (Inscopix, Inc.) during linear track navigation over several days. Hydrocortisone-treated mice exhibited symptoms typically observed during chronic stress, including anhedonia and reduced adrenal and spleen weights. Most properties of place cell function were unchanged in hydrocortisone-treated mice. We trained Bayesian single neuron and ensemble decoders to estimate mouse location on the linear track from neuronal calcium imaging event data. Single neuron decoder performance was

lower in hydrocortisone-treated mice compared to Citalopram-treated mice. Unlike the single neuron decoder, ensemble decoder performance, which estimates mouse location based on the entire population of imaged cells, was unaffected by drug treatment. The dysfunction observed at the single-neuron level indicates that chronic stress may impair the ability of the hippocampus to encode neural representations and memories of the animal's spatial location, a function pivotal in forming an accurate navigational map of the animal's external environment. However, the hippocampal ensemble as a whole is resilient to any hydrocortisone-induced insults to single neuronal place cell function on the linear track.

**Disclosures:** **T. Indersmitten:** Other; Janssen Pharmaceutical Companies of Johnson & Johnson, Inscopix, Inc. **M. Schachter:** Other; Inscopix, Inc. **R. Wyatt:** Other; Janssen Research & Development. **N. Welty:** Other; Janssen Research & Development. **S. Young:** Other; Janssen Research & Development. **S. Campbell:** Other; Janssen Research & Development. **S. Otte:** Other; Inscopix, Inc. **J. Nassi:** Other; Inscopix, Inc. **P. Bonaventure:** Other; Janssen Research & Development.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.08/UU40

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Mechanisms of synchronization of hippocampal oscillations

**Authors: *K. SAFARYAN**[1], M. R. MEHTA[1,2,3,4]
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**Abstract:** Hippocampal neural activity is modulated by several rhythms, including theta, beta, gamma and sharp-wave ripples. These oscillations are shown to be crucial for learning and memory by modulating hippocampal single unit and population responses. In particular, hippocampal theta modulation is especially prominent during active exploration, when spike timing of hippocampal pyramidal cells is robustly encoded by theta phase. In turn, this temporal code is thought to be crucial for inducing synaptic plasticity via STDP (Mehta et al., 2002). Hence, for a better understanding hippocampal learning and memory it is important to understand the mechanisms that regulate the frequency of theta rhythm and its long-range synchronization across hippocampus.
The frequency of theta oscillations increases with running speed when rats run on a linear track in the real world. In contrast, we recently showed that when rats ran in virtual reality, the frequency of theta rhythm does not increase with running speed (Ravassard et al., 2013). Yet,

theta phase precession is comparable between one dimensional real world and one dimensional virtual reality. Further, in two dimensional real world, hippocampal neurons showed significant phase precession during passages through the place field, and this passage-dependent phase precession was intact in two-dimensional virtual reality despite the impaired spatial selectivity (Aghajan et al., 2015). We hypothesized that these differential patterns of hippocampal activity could arise due to difference in synchronization of theta oscillations in the real world and virtual reality. To test this, we measured the hippocampal activity across multiple recording sites while rats ran in real and virtual worlds. We then developed analysis methods that can provide unbiased estimates of synchrony of theta fluctuations across different sites of recording. The results show significant differences in synchronization of low-frequency oscillations as a function of real or virtual tasks.

**Disclosures: K. Safaryan:** None. **M.R. Mehta:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.09/UU41

**Topic:** H.01. Animal Cognition and Behavior

**Title:** A generalized linear model approach to dissociate object-centric and allocentric directional responses in hippocampal place cells

**Authors: *M. SHAHI**[1,2,3,4], R. SANDLER[1,2,3,4], S. DHINGRA[1,2,3,4], R. RIOS[1,2,3,4], C. VUONG[1,2,3,4], L. ACHARYA[6], A. HACHISUKA[1,2,3,4], M. R. MEHTA[1,2,3,4,5]
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**Abstract:** Primate and human hippocampal neurons show visually evoked, object-centric responses. But, visual cues are thought to generate allocentric responses in the rodent hippocampus.
Furthermore, it has been commonly believed that head direction does not influence hippocampal single units during 2D random foraging in the rodent hippocampus. However, our group has demonstrated significant allocentric head direction modulation (Acharya et al., 2016).
This raises an important question: do rodent hippocampal place cells also exhibit object-centric responses, as seen in primates? To address this, we measured hippocampal place cell responses while rats were doing a random foraging task on an open platform in the real world, with one prominent, 10 degree wide visual cue on one wall. We then developed generalized linear model (GLM) technique to decipher the hippocampal responses in the allocentric (room) frame, or in the object-centric (with respect to the visual cue) frame. These two variables are highly

correlated; hence we developed analysis methods to dissociate their respective contributions to CA1 place cells.
However, in this condition, there is only a small difference between the object-centric and allocentric frames. To dissociate this further, we suspended a prominent visual cue above the maze, while rats foraged for randomly scattered rewards, regardless of the visual cue. We then estimated the independent influence of object-centric and allocentric head direction on hippocampal responses, along with the contribution of position and running speed. The method also provided an estimate of the relative magnitudes of these variables. One-third of hippocampal neurons showed significant directionality in the object-centric frame with respect to the visual cue. Moreover, analysis of the object-centric directionality of individual of neurons showed that the ensemble of object-centric maps was tuned towards the visual cue.
These results thus provide novel insights about the mechanisms governing place cells, and have important implications for theories of hippocampal function.

***Bibliography***

Acharya, Lavanya, et al. "Causal Influence of Visual Cues on Hippocampal Directional Selectivity." *Cell* 164.1 (2016): 197-207.

**Disclosures: M. Shahi:** None. **R. Sandler:** None. **S. Dhingra:** None. **R. Rios:** None. **C. Vuong:** None. **L. Acharya:** None. **A. Hachisuka:** None. **M.R. Mehta:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.10/UU42

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Visual cues evoke object-centric directional tuning across the entire hippocampal place cell ensemble

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**Abstract:** Hippocampal CA1 cells show allocentric spatial selectivity, which has been extensively investigated since 1971. We recently showed the presence of directional selectivity in the CA1 cells during random foraging in the real and virtual worlds (Acharya et al., 2016). In this work, using novel experimental and analytical techniques, we have been able to disentangle

the contribution to the directionality of the CA1 cells from the two independent frames of reference - one that is aligned with the room, i.e. the allocentric frame, and the other that is centered on the rat's body, i.e. the object-centric frame (see Shahi et. al. SfN abstract, 2017). The tasks used in this work involved random foraging on an open platform in 2D environments, in Real World (RW) and Virtual Reality (VR), where only distal visual cues are provided, without any reward association to these cues. One such task had one prominent 10 degree wide visual cue on one wall far away from the platform, while the other had a similarly sized and shaped visual cue suspended above the platform. Depending on the nature of the visual cues provided in the room, we can dissociate the allocentric and object-centric tuning of the cells, which under some conditions might not be possible. For analyzing the data, we make use of generalized linear model (GLM), which provides an estimate of the independent contributions from different tuning parameters, such as position, allocentric and object-centric directionality, speed etc. Firstly, we find overlapping, yet slightly different, population of neurons in CA1 which exhibit spatial, allocentric and object-centric tuning to visual cues. Secondly, with only a visual cue on the wall, the contributions from the allocentric and object-centric frames on the tuning of the cells are highly correlated and cannot be dissociated. On the other hand, with the cue suspended above the platform, the contributions from the two frames can be easily dissociated, and about a third of the population responds individually to the two frames in RW. These responses change drastically in the VR, where majority of the spatial and allocentric directional tuning is lost, and about half of the population responds to the object-centric frame of reference. Thirdly, we find that for environments with the suspended cue, the object-centric responses are ensemble-wide, with not only the significant, but even the non-significant cells' responses are tuned towards the suspended visual cue. These results show that contrary to common belief, distal visual cues not only generate allocentric responses, but are also sufficient to generate object-centric responses in CA1, in individual cells and across the entire ensemble.

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**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.11/UU43

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Rapid increase in navigational performance and hippocampal neural activation during a virtual water maze task

**Authors: *M. R. MEHTA**[1,2,3,4], J. J. MOORE[1]
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**Abstract:** The Morris Water Maze is a widely-used behavioral test of spatial learning, memory and navigation. Yet the neural basis of this behavior is not well characterized, because it is difficult to do single unit recordings in this task and because animals typically do few trials in a day which makes robust statistical analysis difficult. Hence, we have recently developed a noninvasive virtual water maze task [1]. With this system, rats can run more than 100 trials in a single session, which allows us to measure within-session changes in behavior and the underlying neural coding mechanisms. Despite good navigational performance in this task, we find relatively little allocentric spatial selectivity in pyramidal units in dorsal CA1, the traditional "Place Cells." Instead, neural activity is tuned to other navigationally-relevant, egocentric parameters, e.g. distance traveled, heading direction, linear speed, and angular speed [2]. Here, we investigate within-session changes in behavioral performance and neural activity. Extensive studies have shown that hippocampal neural activity is altered with experience, with a significant increase in the number of active neurons [3] and their firing rates [4, 5] within the first few trials, even in a familiar environment [3,4, 5]. However, these were done in the absence of task demand.We find that during the virtual navigation task, behavioral performance improved rapidly within the first 5-10 trials each day, even though rats were well-trained on the task. Simultaneously, the mean firing rate of CA1 pyramidal neurons and the total number of neurons active also increased. Finally, behavioral performance was positively correlated with neural activation and firing rate. Thus, even though there is little allocentric spatial selectivity in the hippocampus during this task, experience-based changes in the egocentric neural activity are correlated with experience-based improvements in behavior. These experience-based changes may be driven by similar mechanisms of synaptic plasticity [4,5] demonstrated in earlier studies on linear tracks [3, 4, 5], thus linking behavioral learning with hippocampal activity and cellular mechanisms of plasticity. 1. JD Cushman et al. PLoS One (2013). 2. JJ Moore et al. SfN Abstract #263.03 (2016). 3. MR Mehta, BL McNaughton, NIPS, 741-745, (1997). 4. MR Mehta, CA Barnes, BL McNaughton PNAS 94, 8918-8921 (1997). 5. MR Mehta, MC Quirk, MA Wilson Neuron 25, 707-715 (2000).

**Disclosures: M.R. Mehta:** None. **J.J. Moore:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.12/UU44

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Large, sustained, dendritic depolarizing events in freely behaving rats

**Authors: *J. J. MOORE**[1,2,3,4], M. R. MEHTA[1,2,3,4,5]
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**Abstract:** Neural dendritic arbors make up the majority of surface area and volume of neocortical neurons, but most information about neural activity in freely behaving animals is obtained through extracellular action potentials. *In vitro* studies have demonstrated that dendrites support nonlinear integration of inputs via sodium spikes and calcium spikes [1, 2]. Measurements in anesthetized, head-fixed animals support these findings and suggest that dendritic nonlinearities may affect neural activity *in vivo* [3]. We recently reported the first chronic electrical measurements of dendritic membrane potential in unanesthetized, freely-behaving rats [4, 5]. In those experiments, we observed dendritic action potentials (DAP) firing at high rates, that were modulated by subthreshold fluctuations that were many times larger than the accompanying DAP. Dendritic subthreshold fluctuations and DAP in posterior parietal cortex, a major neocortical input to the hippocampal-entorhinal system, also encoded egocentric representations of movement with a similar degree of precision compared to somatic spikes. The presence of these two very different but interacting signals suggests a mixture of analog and digital coding in the dendrites. Here, we investigate the structure of these large, slow fluctuations.

We observed that the slow subthreshold fluctuations were not random, but contained large, discrete events of sustained depolarization during slow-wave sleep. These depolarizations were approximately 50 ms in duration, similar in duration to calcium spikes reported *in vitro*, but in many instances persisted for several seconds. While DAP fired at rates far exceeding those of somatic spikes detected extracellularly, large depolarizations occurred at lower rates, typically < 1 Hz. Large depolarizations were also present during active running, and they contributed to the subthreshold representation of egocentric movement in posterior parietal cortex. The coexistence and interaction between high-rate, medium-amplitude DAP and low-rate, high amplitude depolarizations suggests that dendrites may encode complimentary information through different mechanisms. These different nonlinearities may also control the spatial extent of integration in the dendritic tree in a dynamic fashion.

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**Disclosures: J.J. Moore:** None. **M.R. Mehta:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.13/UU45

**Topic:** H.01. Animal Cognition and Behavior

**Support:** GACR 15-20008S

Progres Q39

NPU I LO1503

**Title:** Memory recall induced hyperactivity of place cell populations in hippocampal CA3

**Authors: *F. ZITRICKY**, K. JEZEK
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**Abstract:** Hippocampal autoassociative network in CA3 stores large number of place cell activity patterns that are believed to be a substrate of spatial memories. They behave as network activity states with attractor properties. Memory recollection on the network level is then conceptualized as a shift from whatever present activity pattern towards another state that reflects the actual input information. Mechanisms underlying this process are largely unknown. We examined development of CA3 population activity during retrieval of memory for spatial context in rats using 'teleportation' protocol, where memory recall was induced by a sudden switch between two sets of distinct light cues defining two familiar environments. Previous study described the competitive nature of spatial map transition with network state temporarily alternating in a theta paced manner between the original (old) and correct (new) representation. Here we report a new effect of transient hyperactivity (approx. 30% increase) in CA3 hippocampal network accompanying the recall of stored hippocampal representation. The hyperactivity was driven by an increased recruitment of place cells per theta cycle, rather than an increase of spiking activity only and it persisted for few seconds before it dropped back to baseline level. Considerably, hyperactivity in the network selectively occurred only during expression of the correct representation as it didn't accompany an occasional reactivation of the original spatial map. We found that this effect was driven mainly by an increased recruitment of place cells at the periphery of their firing fields. In consequence, decoded momentary spatial position from the new representation ensemble activity rendered an increased coding error. Despite the expression of both network states showed an attractor-like behavior, teleportation experience substantially increased emergence of data bins where cells from both 'old' and 'new' ensembles mixed together.
We show that network recall of spatial memory state triggers a transitory hyperactivity of CA3 neuronal population. Temporary conflict of sensory input may contribute to altered spatial

properties of place cells shortly after introduction of the new environment. We argue that enhanced, albeit less position-specific recruitment of place cells may support the new representation in competition with the original ensemble, and possibly reinforce transition between the corresponding attractor states.

**Disclosures: F. Zitricky:** None. **K. Jezek:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Support:** NIH Grant R01 NS39456

NIH Grant R01 MH094146

International Human Frontier Science Program Organization LT00683/2006-C

**Title:** Egocentric bearing selectivity in lateral entorhinal cortex

**Authors: *X. CHEN**[1,2], C. WANG[1,2], H. LEE[1,2], G. RAO[1,2], D. YOGANARASIMHA[3], F. SAVELLI[1,2], J. J. KNIERIM[1,2,4]
[1]Johns Hopkins Univ., Baltimore, MD; [2]The Zanvyl Krieger Mind/Brain Inst., Baltimore, MD; [3]Natl. Brain Res. Ctr., Haryana, India; [4]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

**Abstract:** The lateral entorhinal cortex (LEC) and medial entorhinal cortex (MEC) provide the major inputs to the hippocampus, which plays an essential role in spatial and episodic memory. The discovery of cell types with various spatial properties in MEC, e.g, grid cells, greatly enhances our understanding of functional circuitry in the medial temporal lobe. However, much less is known about the function of LEC. Previous studies showed that cells in LEC carry much less spatial information than MEC, but the introduction of objects in the arena significantly increases the spatial information content of LEC neurons. We investigated whether other behavioral variables, e.g. head direction, can modulate the firing of LEC neurons. We recorded 68 LEC cells in 2 rats and 111 MEC neurons in 3 rats, in which the subjects were foraging freely in an open-field arena. The experiment was first performed while the subjects foraged in a 0.58-m x 0.58-m box in the center of a 1.35-m x 1.35-m box. The walls of the small box were removed after 6 minutes and rats were able to navigate freely in the large box. We found a large number of LEC neurons showed egocentric bearing selectivity relative to certain reference points in the arena. Most of the reference points were close to the center of the box, and the egocentric bearing selectivity was manifested as preferences for clockwise, counterclockwise, inward, or

outward movement relative to the center. We applied a Generalized Linear Model (GLM) to account for the potential confounds introduced by uneven sampling of head direction and space. Models with (a) conjunctive spatial and egocentric bearing tuning around an external reference point and (b) with conjunctive spatial and allocentric head direction tuning were fit to the data. LEC neurons were significantly different from MEC cells ($p < 0.001$, Wilcoxon rank-sum test), with LEC neurons showing a greater preference for egocentric bearing than allocentric head direction tuning ($p < 0.001$, Wilcoxon signed-rank test) and MEC cells showing a greater preference for allocentric head direction ($p < 0.001$, Wilcoxon signed-rank test). These results show that LEC neurons carry information about the rat's current movement behavior relative to an external location in an egocentric framework, suggesting the "what" versus "where" dichotomy for explaining the functions of LEC and MEC needs a major revision. We hypothesize that while MEC mainly represents spatial information about the location of "self", LEC conveys information about "non-self" ("what is out there") (Lisman 2007; Knierim et al. 2014).

**Disclosures: X. Chen:** None. **C. Wang:** None. **H. Lee:** None. **G. Rao:** None. **D. Yoganarasimha:** None. **F. Savelli:** None. **J.J. Knierim:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

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**Program#/Poster#:** 523.15/UU47

**Topic:** H.01. Animal Cognition and Behavior

**Support:** R01 MH094146

R01 NS039456

**Title:** Surface texture boundaries alter firing rates of CA1 place cells in 2-dimensional environments

**Authors: *C.-H. WANG**, G. RAO, J. J. KNIERIM
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**Abstract:** Surface textures have been used to examine the influence of local cues over place-cell firing. Manipulations of differently-textured surface patches (e.g., rotation or reconfiguration of the patches) can lead to corresponding place field rotation, rearrangement, or remapping (Shapiro et al., 1997; Brown and Skaggs, 2002; Knierim, 2002). However, these studies have not addressed how local surface boundaries can alter the structure of the spatial representations of the larger environment. In a heterogeneous environment composed of differently textured surfaces, the space can be demarcated by the boundaries between different textures and

segmented into different compartments. We therefore hypothesized that the surface boundaries are encoded in the cognitive map and influence the precise firing locations of place cells. We previously reported that both CA1 and CA3 place fields tend to terminate near texture boundaries when rats foraged on a circular track (Wang et al., SFN Abstracts, 2016). To further study this phenomenon, we recorded the activity of place cells as rats foraged in 2-dimensional open fields with discrete surface textures and tape lines defining geometric shapes and boundaries. We first collected data from 5 rats on a 1 x 1 m platform with a complex pattern of shapes and boundaries. The platform was divided in half along its diagonal. One half was covered by textured patches (such as sand paper, rubber mats, and cork material) and the other half replicated the same geometric pattern by outlining the shapes with yellow tape. Anecdotal observations indicated that the edges of many CA1 place fields coincided with the boundaries, and a small proportion of fields appeared to match the geometric shapes on the platform. However, the complexity of the pattern and the large number of boundaries on the board limited the ability to perform quantitative analyses of this data set. Thus, we recorded from 2 additional rats on a simple 1 x 1 m platform containing only two texture patches separated by a single linear boundary. The CA1 place cell populations had stronger average firing rate changes near the boundary than at locations away from the boundary. These results suggest that CA1 spatial representations emphasize surface boundaries in the environment, which may enable segmentation/compartmentalization of experiences by natural environmental boundaries.

**Disclosures: C. Wang:** None. **G. Rao:** None. **J.J. Knierim:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.16/UU48

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant R01 MH094146

NIH Grant R01 NS39456

**Title:** Influence of objects on egocentric bearing tuning in lateral entorhinal cortex

**Authors: *C. WANG**[1,2], X. CHEN[1,2], S. S. DESHMUKH[3], J. J. KNIERIM[1,2,4]
[1]Johns Hopkins Univ., Baltimore, MD; [2]The Zanvyl Krieger Mind/Brain Inst., Baltimore, MD; [3]Ctr. for Neurosci., Indian Inst. of Sci., Bangalore, India; [4]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

**Abstract:** In a companion abstract (Chen, Wang, et al., SFN Abstracts, 2017), we show that lateral entorhinal cortex (LEC) neurons are significantly more selective for egocentric bearing

relative to an external reference point than medial entorhinal cortex (MEC). Those experiments did not address whether there were any biases for particular external locations to serve as reference points. We predicted that behaviorally relevant locations would be over-represented as reference points for egocentric tuning in LEC but not in MEC. Two experiments were performed to test this prediction. In Experiment 1, 159 LEC unit recordings and 111 MEC unit recordings were obtained while 7 rats foraged freely in a 1.2-m x 1.5-m open field with multiple objects placed inside the arena. A Generalized Linear Model (GLM) was applied to remove spurious tuning which could arise from biased trajectory and spatial selectivity. LEC cells demonstrated significantly more egocentric bearing tuning around certain reference points than MEC cells ($p < 0.001$, Wilcoxon rank-sum test). We then used the locations of the objects as reference points and found that LEC neurons showed significantly more egocentric bearing relative to objects than MEC cells ($p < 0.001$, Wilcoxon rank-sum test). In Experiment 2, 199 recordings were obtained while 2 rats navigated in a 1.37-m x 1.37-m box with a fixed food well. Food reward was available sporadically in the food well and at random unmarked locations in the arena. The position of the food well was manipulated across sessions. For the cells with the largest egocentric bearing tuning relative to some locations, we found a significant overrepresentation of the current or previous goal location compared to an expected random distribution ($p < 0.001$, Monte Carlo simulation test). A number of cells shifted their reference points with the food well. These results provide strong evidence that LEC represents egocentric bearing information about behaviorally relevant locations away from the subject. Thus, in addition to nonspatial information about “what” the animal experiences during an event, LEC also represents “where” information in an egocentric frame of reference that is fundamentally different from the predominantly allocentric spatial representations of MEC.

**Disclosures:** **C. Wang:** None. **X. Chen:** None. **S.S. Deshmukh:** None. **J.J. Knierim:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

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**Topic:** H.01. Animal Cognition and Behavior

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NIH Grant R21 NS095075

Johns Hopkins University Discovery Award

Kavli Neuroscience Discovery Institute Postdoctoral Fellowship

**Title:** Recalibration of the path integrator in virtual reality as revealed in CA1 place cells

**Authors: *M. S. MADHAV**[1], R. P. JAYAKUMAR[2], F. SAVELLI[1], M. BREAULT[3], H. T. BLAIR, IV[4], N. J. COWAN[2], J. J. KNIERIM[1]
[1]Mind / Brain Inst., [2]Dept. of Mechanical Engin., [3]Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [4]Dept Psychology, UCLA, Los Angeles, CA

**Abstract:** The rodent hippocampal formation combines information from both landmark and self-motion cues to create an allocentric representation of its environment. We used a planetarium-style virtual reality dome to examine the relative influence of these two classes of information on the firing fields of place cells.
We tested whether the brain recalibrates the relationship between self-motion cues perceived by the rat during movement, and the update of the position encoded by CA1 place cells. We call this relationship the 'internal gain' of the path integrator (r), and hypothesize that this is a plastic variable learned via feedback from landmark cues.
Previously (Jayakumar et al., 2016, Madhav et al., 2015, SFN Abstracts) we presented evidence from experiments in which a constellation of visual landmarks was rotated continuously as a ratio of the rat's movement speed along the perimeter of a circular platform. This ratio was called the experimental gain (g). We observed that CA1 place fields 'locked' to the landmarks (N = 5 rats), indicating that the visual landmarks exerted a strong influence on the hippocampal representation of place. However, in the absence of landmarks, place fields gradually drifted, reflecting cumulative path integration error. This drift was the same across simultaneously recorded place cells, revealing a cohesive representation of position amenable to population decoding.
Here, we investigated whether the internal gain (r) of the path integrator could be recalibrated by continuous exposure to an experimental gain (g) of the landmarks relative to the rat's movement. At the beginning of an experiment, g was set to zero (stationary landmarks), but gradually increased or decreased to a certain value (processing / precessing landmarks) that subsequently remained constant (for ~30 laps, < 1 hour). Using a decoding technique based on the spatial frequency of place fields, we confirmed quantitatively that the place fields were locked to the landmark frame of reference. When the landmarks were turned off, the place fields drifted relative to the landmark frame. Through the same decoding technique, we estimated the effective internal gain (r) of the place field ensemble and showed that the internal gain had a value in the same direction as the experimental gain but lower in magnitude ( $0 < |r| < |g|$ ). Indeed, this recalibrated gain (r) of the place fields maintained a linear relationship to the experimental gain (g) of the landmarks (N = 4 rats). These results indicate that visual landmarks calibrate how self-motion cues are integrated to update the hippocampal representation of place, and this calibration occurs over relatively small time scales.

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**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.18/UU50

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Preconfigured, plastic networks: Unified view on integration of Hebbian and homeostatic processes during learning

**Authors: *G. DRAGOI**, U. FAROOQ, J. SIBILLE, K. LIU
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**Abstract:** The demonstration that hippocampus is crucial for rapid learning and memory formation in humans, non-human primates and other species, most notably rodents, has sparked a major, concerted effort toward identification of electrophysiological signatures underlying these cognitive functions. Electrophysiological signatures of hippocampus role in learning and memory were successively attributed to post-experience increases in spontaneous firing rate, neuronal cofiring, and incidence of spatial sequence and trajectory replay. The temporal sequence hallmark for learning has, however, remained equivocal, with proposals ranging from de novo Hebbian creation of temporal sequences from blank-slate networks to selection and editing of largely homeostatic preconfigured sequences. Here we show that de novo spatial experiences essentially induce Hebbian firing rate and cofiring increases within neuronal ensembles, which are integrated into largely stable, homeostatic ensemble temporal dynamics expressed similarly pre- and post-experience. Furthermore, we demonstrate that former proposals of pre-experience blank-slate networks using sequence analyses falsely arise from incorrect statistical assumptions and offer solutions to amend them. Our results coherently unify previously divergent views of ensemble signatures of learning and memory and provide strong support for hippocampal preconfigured, plastic networks that integrate Hebbian learning within largely homeostatic processes.

**Disclosures:** **G. Dragoi:** None. **U. Farooq:** None. **J. Sibille:** None. **K. Liu:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.19/UU51

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Ontogeny of ensemble spatial representation in the hippocampus

**Authors: *U. FAROOQ**, G. DRAGOI
Yale Univ., New Haven, CT

**Abstract:** Hippocampal pyramidal cells - known as 'place cells' - are active in distinct, specific locations along the trajectory of the animal during locomotion within an environment. Populations of place cells exhibit temporal coordination beyond their single cell response characteristics by firing in compressed temporal sequences during motion, awake rest and sleep. These sequential population phenomena (i.e. theta sequences, replay and preplay) are widely considered as the neural substrates for spatial cognition, and episodic memory formation and consolidation in adult animals. Recent work has shown that place cells are already present when rodents ethologically begin to exhibit behaviors involving extended forays out of their nest (in the beginning of third postnatal week), albeit their metrics of spatial tuning improve with age and experience over the next couple of weeks. Intriguingly, the upstream entorhinal grid cells emerge later and have a delayed developmental timeline compared to place cells. Whether and when ensembles of place cells can display different sequential population phenomena at these ages remains unknown. To this end, we performed high-density *in vivo* electrophysiology in freely moving pre- and post-weanling rats throughout the third and fourth weeks of development and recorded simultaneously from up to 70 CA1 hippocampal neurons during active behaviors on novel linear tracks, and pre- and post-experience sleep. Our experiments have enabled us to probe the developmental stages of ensemble spatial representation in the hippocampus and provide insights into how the first traces of episodic memories are being formed in the brain.

**Disclosures: U. Farooq:** None. **G. Dragoi:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.20/UU52

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Generative predictive codes for future place cell sequences during pre-experience sleep

**Authors: *K. LIU**, J. SIBILLE, G. DRAGOI
Yale Univ., New Haven, CT

**Abstract:** Mammalian navigation uses internal models to predict and represent the spatial-temporal statistical regularity of the sequence of environmental locations. The internal representation process has been described in rodents by the sequential activation of neuronal

ensembles of ‘place cells’ in the hippocampus, which together form a ‘cognitive map’ of the external world. Attractor-network models of hippocampal activity during animals’ spatial exploration have suggested that place cell assemblies can be used to represent locations in any arbitrary environments via auto-associative dynamics during theta oscillations. Hippocampal-dependent internal representations are believed to emerge upon transitions from auto-associative attractor networks representing discrete locations into hetero-associative sequential attractors representing temporally-compressed trajectories, particularly in association with 200 Hz oscillations ‘ripples’. These transitions occur spontaneously during epochs of awake immobility and slow-wave sleep and can replay past and preplay future trajectories at ~20 times accelerated, 5-8 m/s velocities. Previous research leveraged on the activity expressed during a novel navigation experience to seek for correlative temporal sequence patterns in the following (replay) and preceding (preplay) rest and sleep epochs. Consequently, the predictive capacity of hippocampal networks during sleep/rest and their spontaneous organization into associative attractors that lead to networks active during future spatial navigation have remained unknown. Here, we develop a novel predictive coding model to reveal the internal structure of functional neuronal connectivity exclusively during pre-experience sleep in naïve rats and use the connectivity probability to predict the future place cell sequences during subsequent encoding of novel spatial experiences. We find that connectivity probability during preceding sleep has significant predictive value over future sequential activity during run while post-experience sleep exhibits a higher prediction performance. These results indicate that neuronal sequence activity expressed during a future novel experience can be generated based on intrinsic connectivity probability that is further refined during and after the experience.

**Disclosures:** **K. Liu:** None. **J. Sibille:** None. **G. Dragoi:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** New York Stem Cell Foundation

Simons Foundation

NIMH MH106475

**Title:** Grid scale drives the scale and long-term stability of place maps

**Authors:** ***C. S. MALLORY**[1], K. HARDCASTLE[2], J. S. BANT[1], L. M. GIOCOMO[1]
[1]Neurobio., Stanford Univ., Stanford, CA; [2]Neurobio., Stanford Univ., Palo Alto, CA

**Abstract:** Medial entorhinal cortex (MEC) grid cells fire at regular spatial intervals and project to the hippocampus, where place cells are active in spatially restricted locations. A cardinal feature of the grid population is the increase in grid scale along the dorsal-ventral MEC axis. However, the difficulty in perturbing grid scale without impacting the properties of other functionally-defined MEC cell types has obscured how grid scale influences hippocampal coding and spatial memory. We used a targeted viral approach to knock out HCN1 channels selectively in MEC, causing grid scale to expand while leaving other MEC spatial and velocity signals intact. Grid scale expansion resulted in place scale expansion predominantly in fields located far from environmental boundaries and reduced long-term place field stability. To better understand the mechanism through which grid scale influences long-term place field stability we implemented a computational model of place cell formation, in which place fields are formed via a winner-take-all competition. In the model, place cells received two types of input: modular grid cell inputs, whose firing field locations remained static across days, and non-stable spatial inputs whose preferred firing location varied from day to day. Recapitulating our experimental findings, the stability of place fields declined as the scale of the grid input increased. Mechanistically, the combined input from smaller-scale grid cells tended to overlap more in space, rendering the resulting place fields more resistant to fluctuations in other types of spatial inputs, and ultimately more stable across sessions. Finally, we found that spatial memory was impaired in these mice, likely due to the decreased long term stability of their place cells. Together, these experiments illuminate how grid scale impacts place coding and spatial memory.

**Disclosures: C.S. Mallory:** None. **K. Hardcastle:** None. **J.S. Bant:** None. **L.M. Giocomo:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** New York Stem Cell Foundation

Simons Foundation

NIMH MH106475

**Title:** Coordinated modulation of grid and speed cells by self-motion cues

**Authors: *M. G. CAMPBELL**[1], C. S. MALLORY[2], L. M. GIOCOMO[2]
[2]Neurobio., [1]Stanford Univ., Stanford, CA

**Abstract:** To calculate self-location, the brain must integrate multi-sensory cues regarding environmental landmarks and the animal's motion relative to those landmarks. The medial entorhinal cortex is a proposed locus for the calculation of position, with different cell types integrating different combinations of self-motion and landmark cues. In particular, grid cells are thought to integrate self-motion cues (path integration), whereas border cells are thought to respond to environmental landmarks. However, the mechanism by which self-motion influences grid cells, as well as the way in which diverse self-motion cues are combined (e.g., visual and locomotor), is not well understood. To study these questions, we recorded entorhinal cells during exploration of a virtual linear track and manipulated the gain of the closed-loop transformation from locomotion to motion of the visual cues. These experiments revealed that grid cells integrate self-motion cues whereas border cells remain fixed to visual landmarks. Furthermore, they enabled us to calculate the relative weighting of visual and locomotor cues in grid and speed cell tuning curves and showed that this weighting is condition-dependent. Finally, in response to the gain manipulations, the speed and grid tuning of conjunctive grid-speed cells were significantly correlated, but the speed and grid cell populations as a whole were uncorrelated. This suggests that only a subset of linear speed signals in the MEC is relevant for grid cell distance calculations.

**Disclosures: M.G. Campbell:** None. **C.S. Mallory:** None. **L.M. Giocomo:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

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**Topic:** H.01. Animal Cognition and Behavior

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New York Stem Cell Foundation

Simons Foundation

NIMH MH106475

**Title:** Environmental deformation causes commensurate changes in grid, head direction, and speed cells in entorhinal cortex

**Authors: *R. G. MUNN**[1], C. MALLORY[1], D. M. CHETKOVICH[2], L. M. GIOCOMO[1]
[1]Neurobio., Stanford Univ., Stanford, CA; [2]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

**Abstract:** The tessellating firing fields of grid cells in the medial entorhinal cortex (MEC) are thought to underlie the ability of animals to determine distance travelled and navigate through space. Exactly how these cells gain their firing characteristics remains to be fully understood. Continuous attractor models are a leading model for grid cell formation. These models propose that directional and speed inputs could combine to translate the activity pattern across the grid cell network (Burak and Fiete, 2009). In these experiments, we rapidly compressed or expanded an open arena along one axis while recording single unit activity in the MEC of mice. This type of environmental deformation has been shown to change grid cell spacing (the distance between grid cell firing nodes). Grid spacing decreases or increases along the axis that is compressed or expanded, but is preserved in the orthogonal, invariant axis (Barry et al., 2007). In continuous attractor models, grid spacing can be driven by the amplitude of the directional and speed signals, a hypothesis we tested by recording grid, head direction and speed cells prior to, and during environmental deformation. For environmental compression, we found that the length of the directional vector decreased in the majority (~65%) of MEC head direction cells (average decrease = 38.2%) and became significantly less directionally stable. The remaining ~35% of head direction cells increased in vector length by an average of 163.5%, while maintaining their directional stability. We found that the head direction cells that increased directional specificity were bimodally distributed, with preferred firing orientations that are closely aligned with the axis of deformation. On the other hand, cells that decreased in specificity had preferred firing orientations in all directions. Similarly, MEC speed cells preferentially modulated the gain of their firing rate/running speed relationship in the direction of environmental deformation. Ongoing work is examining whether head direction and speed signals respond in a complementary manner during environmental expansion. These findings are broadly in support of predictions made by the continuous attractor model that speed and directional inputs can drive the translation of the neural sheet, and thereby drive grid cell spacing.

**Disclosures:** **R.G. Munn:** None. **C. Mallory:** None. **D.M. Chetkovich:** None. **L.M. Giocomo:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

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**Support:** New York Stem Cell Foundation

Simons Foundation

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**Title:** Grid symmetry and bursting along the dorsoventral axis of medial entorhinal cortex

**Authors: *J. S. BANT**, K. HARDCASTLE, L. M. GIOCOMO
Neurobio., Stanford Univ., Stanford, CA

**Abstract:** Neurons in the medial entorhinal cortex (MEC) encode spatial location, head direction, and speed (Hafting et al., 2005; Sargolini et al., 2006; Kropff et al., 2015), signals that may benefit from the higher information transfer rates conferred by high-frequency bursts of activity. Previously we reported that fractions of non-inactivating voltage-gated sodium conductances, which play a key role in the genesis of high-frequency activity, are higher in the dorsal end of MEC. (Bant and Giocomo, SfN 2015; Bant and Raman, 2010). This generates the in vivo prediction that cells in dorsal MEC will fire at higher frequencies than cells in ventral MEC. To test this prediction, we considered a set of 837 layer II/III putative excitatory MEC neurons recorded as mice explored large open arenas. First, we examined grid cells, which can fire high-frequency bursts that reach over 300 spikes/s, some of the fastest firing of excitatory cells reported in cortex. As a population, grid cells had significantly higher bursting values (% of ISI < 10 ms) compared to border or head direction cells, consistent with recently published work on the inter-spike interval differences amongst these populations of cells (grid = 8.2 ± 0.6%; border = 4.0 ± 0.4%; head direction = 5.6 ± 0.3%) (Latuske et al., 2015). Interestingly, as predicted by our in vitro voltage-clamp and current clamp data on specialized Na current kinetics and propensity to burst, bursting percentage across the grid cell population decreased as a function of dorsal-ventral depth ($r = 0.15$, $p < 0.001$). This dorsal-ventral organization in bursting percentage was not present in head direction cells ($r = 0.02$, $p = 0.76$) or border cells ($r = 0.17$, $p = 0.12$). Functionally, bursting significantly correlated with grid symmetry, as well as the stability and coherence of grid patterns, suggesting that bursting in grid cells enables robust spatial coding. This increased spatial fidelity in bursting grid cells, compared to non-bursting grid cells, occurred across multiple running speeds and became more pronounced at very high running speeds. Combined, these data raise the possibility that the gradient in sodium current kinetics is related to the emergence of a grid cell population that codes robustly at high speed. Ongoing analyses aim to address the mechanistic relations between speed, coding accuracy, and bursting as we connect intrinsic conductances that vary across the dorsal-ventral axis of MEC to a functionally important burst coding gradient in vivo.

**Disclosures:** **J.S. Bant:** None. **K. Hardcastle:** None. **L.M. Giocomo:** None.

**Poster**

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**Title:** Visual task-relevant cues enhance MUA events across hippocampal place cells

**Authors: *I. MILOJEVIC**, J. S. MONTIJN, J. V. LANKELMA, S. I. RUSU, C. S. LANSINK, C. M. A. PENNARTZ
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**Abstract:** While animals are exploring an environment their hippocampal pyramidal cells tend to fire in a spatially specific manner within a small area of space called a “place field”. Furthermore, the hippocampal representation of space is dynamic: place cells can be active outside their classical place fields. In particular, during resting periods in the behavioral task this sequential activity can reflect both previously explored behavioral trajectories and subsequent ones. Complex patterns of hippocampal bursting activity can represent a diversity of spatial trajectories, some of which were classified as replay and some of which were correlated with planning of future events. However, it remains uncertain which cognitive function is subserved these events and what information they encode. To investigate whether visual stimuli can trigger bursting activity reflecting replay or planning-related activity we trained rats on a task which demands activation of neural networks that are collectively capable integration of self-motion information, environmental information (e.g. visual cues) and predictions about future reward. Four Lister-Hooded rats were trained on an automated custom-built maze with easily modifiable, dichotomous trajectories (spatial exploration trajectories, SET). The maze had two observation decks elevated with a respect to a start chamber that was separated from the SET with a sliding transparent door. LEDs were positioned underneath the SET and could be switched on and off at different stages of the trial. The behavioral task was constructed such that rats visually inspected their future paths while one of the two potential trajectories was illuminated by LEDs, indicating the path leading to reward when chosen. We constructed novel SET configurations every three days during recordings.
We obtained ensemble recordings (16 recording tetrodes) from dorsal hippocampus, CA3 area, while rats were engaged in the behavioral task. From isolated single units (total of 831 cell), multiunit activity (MUA) histograms were formed and events of increased MUA activity (IMUA’s) were identified. We investigated occurrences and spatial representation of IMUA intervals. We observed that stimulus onset (SET path illuminated by LEDs) increases IMUA in the hippocampal network. Further, we used a Bayesian decoding algorithm to investigate if place-cell sequence events can be detected in IMUA’s and if they represent replay or prospective events across familiar and novel environments.

**Disclosures: I. Milojevic:** None. **J.S. Montijn:** None. **J.V. Lankelma:** None. **S.I. Rusu:** None. **C.S. Lansink:** None. **C.M.A. Pennartz:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.26/UU58

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Kaken-hi (15H05569)

Kaken-hi (15H01417)

**Title:** Distinct hippocampal place codes for goal-directed behavior in a two-dimensional open field

**Authors: *Y. AOKI**, H. IGATA, T. SASAKI, Y. IKEGAYA
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**Abstract:** Hippocampal place cells show strong goal-directed tuning within their place fields when animals engage in goal-directed behavior. To address the detailed characteristics of goal-directed tuning, spiking patterns of hippocampal cells were recorded while rats performed a goal-directed task where rats were required to run toward a light-cued goal port to obtain a reward in an open field. Enhancing the degree of freedom of moving directions by utilizing the two-dimensional space allowed us to analyze animal's trajectories from various provenance toward goals. A population of hippocampal cells increased their firing rates when the rats approached to a specific goal port, termed goal-directed cells. When switched to the pseudo-random foraging task where the rats freely searched randomly scattered reward in the same field, some of the goal-directed cells fired at the identical locations, termed non-remapped cells, whereas the others exhibited highly differentiated firing fields in the two contexts, termed remapped cells. In the foraging task, the non-remapped cells more strongly fired as the rats passed through the place field at higher running speed toward the previous goal port, indicating that goal-directed signals are integrated onto spatial firing of these cells. These results demonstrate that there are distinct types of hippocampal cell ensembles for encoding goal-directed behavioral contexts.

**Disclosures: Y. Aoki:** None. **H. Igata:** None. **T. Sasaki:** None. **Y. Ikegaya:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.27/UU59

**Topic:** H.01. Animal Cognition and Behavior

**Title:** An examination of the necessity of hippocampus temporal coordination for self-localization in a place accuracy spatial task

**Authors: *J. M. BARRY**[1], P. MOUCHATI[1], P. LENCK-SANTINI[2], G. HOLMES[1], J. L. KUBIE[3]
[1]Neurolog. Sci., Univ. of Vermont, Burlington, VT; [2]2Institut de Neurobiologie de la Méditerranée, INSERM, Marseille, France; [3]Cell Biol., SUNY Downstate Med. Ctr., Brooklyn, NY

**Abstract:** Hippocampal network coordination of the relationship between theta rhythmicity and neuronal firing has been thought to be a critical element for spatial cognition. For example, the precision of place cell firing relative to theta rhythm is thought to enhance place cell accuracy and the navigational ability of the rat. To our knowledge, this hypothesis has not been tested in functional studies. Our preliminary data suggests that while optogenetic stimulation of the medial septum (MS) can adjust the rhythmic frequency of hippocampal theta, and leave the spatial firing of hippocampal neurons intact, it disrupts the coordination between these physiological events. Specifically, we measured the theta phase preference angle and magnitude of place cells during conditions of varying spatial demand, including both cued and uncued versions of the place accuracy navigation task. These cued and uncued sessions coincided with either continuous experimental or control 6 Hz optogenetic MS stimulation. Preliminary results indicate that ensemble levels of place cell phase preference increase during the uncued version of the task in comparison to the cued version of the task. Moreover, experimental MS stimulation abolished place cell phase preference and affected both the behavioral strategy and accuracy of the spatial task. Control MS stimulation did not affect either of these variables in either cued or uncued versions of the task. While further research is necessary, the results indicate the necessity of phase preference, and therefore temporal coordination of neurons in the hippocampal circuit, may be necessary for both self-localization and spatial navigation in the place accuracy task.

**Disclosures: J.M. Barry:** None. **P. Mouchati:** None. **P. Lenck-Santini:** None. **G. Holmes:** None. **J.L. Kubie:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.28/UU60

**Topic:** H.01. Animal Cognition and Behavior

**Title:** The statistics of hippocampal CA1 place field activity in large virtual environments

**Authors: *J. LEE**, J. BRIGUGULIO, S. ROMANI, A. K. LEE
HHMI / Janelia Res. Campus, Ashburn, VA

**Abstract:** The location of an animal within its environment can be decoded from the activity of hippocampal CA1 place cells. In a small environment, most CA1 pyramidal neurons are active at a single location (place field) or not at all (silent cells). Rich et al. (Science 345: 814-7, 2014) reported that, in a large environment (48 m long track), the distribution of rat CA1 place fields was well-described by a gamma-Poisson model such that (1) many cells had few or no place fields while a few cells had many place fields (gamma-distributed), and (2) the place fields of each cell were randomly distributed across the environment (Poisson-distributed). To further examine the properties of place cells and place fields in large environments, we performed 2-photon imaging of hippocampal CA1 neurons in head-fixed, GCaMP6f-expressing transgenic mice (Dana et al. (PLoS One 9:e108697, 2014) running on a spherical treadmill in a visual virtual reality system (Dombeck et al., Nature Neuroscience 13: 1433-40, 2010). Virtual environments were 40 m long and 2-photon imaging allowed the spatially tuned calcium activity of >500 simultaneously imaged cells to be followed over days. This enabled statistical assessment of place field activity and stability at the population level, with implications for both the mechanisms underlying place field generation, as well as the structure of spatial representations.

**Disclosures: J. Lee:** None. **J. Brigugulio:** None. **S. Romani:** None. **A.K. Lee:** None.

**Poster**

**523. Spatial Navigation: Grid and Place Cells**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 523.29/UU61

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Kaken-hi 15H05569

Kaken-hi 15H01417

**Title:** Time-varying reactivated cell ensembles predict place cell firing

**Authors: *S. YAGI**, H. IGATA, Y. SHIKANO, Y. AOKI, T. SASAKI, Y. IKEGAYA
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**Abstract:** Hippocampal pyramidal neurons specifically increase their firing rates when an animal visits a particular location of the environment, termed place cells. In general analyses, firing patterns of place cells have been characterized based on a spatial distribution of firing rates averaged over an entire recording session. A place cell, however, emits variable numbers of

action potentials even when the animal visits the same place field. In this study, we analyzed such trial-to-trial variability of place cell firing recorded from rats performing a linear track task. As a possible source of the variability of place cell firing, we focused on lap-by-lap changes in synchronous reactivation patterns of neuronal ensembles during consummatory periods at a track end. Similar sets of neurons, including both spatial and non-spatial cells, tended to repeatedly participate in neuronal synchrony within a single consummatory period, whereas different neuronal populations emerged in different consummatory periods. A linear regression analysis revealed that such time-varying reactivation patterns of neuronal populations during individual consummatory periods could predict the firing rates of a place cell observed during running immediately after the consummatory periods. The results suggest that place cell firing is not simply triggered by static inputs representing external environments but is subject to time-varying internal states of neuronal populations.

**Disclosures: S. Yagi:** None. **H. Igata:** None. **Y. Shikano:** None. **Y. Aoki:** None. **T. Sasaki:** None. **Y. Ikegaya:** None.

**Poster**

**524. Cognitive Development**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 524.01/UU62

**Topic:** H.02. Human Cognition and Behavior

**Support:** Elizabeth H. Solomon Center for Neurodevelopmental Research.

NSF grant #SMA-1041755 to the Temporal Dynamics of Learning Center (TDLC), an NSF Science of Learning Center

**Title:** Sleep spindle topography in 6.5 month-old human infants is sexually dimorphic, correlated with language measures, and functionally left-lateralized

**Authors: *S. E. PETERS**, A. A. BENASICH
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**Abstract:** Sleep spindles are patterned bursts of oscillatory brain activity, visible in the scalp EEG, associated with NREM sleep, neuroplasticity and cortical development. In adults, spindles are typically defined by a slow or fast frequency, with fast spindles having a predominantly centro-parietal topography. Adult spindles are sexually dimorphic: in females, fast and slow spindle amplitude are positively correlated with IQ, whereas in males, posterior fast spindle density is negatively correlated. Females also show higher spindle activity in the left frontal region, in both adults and infants. Recently, sex-specific patterns of sleep spindles and cognition have been shown in adolescents and children, with fast and slow spindle amplitude and density

correlating with measures of IQ, in females. In infants, spindles are a biomarker of maturation, first appearing about 4-9 weeks of age, reaching peak duration and density between 3 and 6 months-of-age. During this time, infants are developing pre-linguistic auditory cortical maps that support emerging language. Mini-puberty, a burst of gonadal hormones that occurs at about 8 weeks-of-age, concurrent with spindle onset, impacts later language development via positive estradiol and negative testosterone. Might infant sleep spindles comprise a sensitive measure of individual differences in network development, thus contributing to group-level sex differences in neural processing of language? In this study, we mapped the topography of spectral power in the spindle frequency range (10-16Hz), using 124-channel EEG (EGI, Inc.), during daytime naps in a typically developing cross-sectional group of infants aged 3.5-4 and 6.5-7 months. We administered a standardized behavioral assessment, the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), on the same day as the nap recording, allowing us to examine sex-based differences between topographical spindle spectral power and its association to standardized measures of behavior and cognition. Females showed higher spindle-band spectral power in left-lateralized central and frontal electrode clusters. Slow spindle-band power was positively correlated with expressive language in females, whereas fast spindle-band power was negatively correlated with receptive language in males. These data suggest that early language-based neural network development is associated with emerging sleep spindle topography and frequency. We hypothesize that the burst of gonadal hormones during mini-puberty, could be mediating the dimorphic development of sleep spindles and their correlation with language development.

**Disclosures:** **S.E. Peters:** None. **A.A. Benasich:** None.

**Poster**

**524. Cognitive Development**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 524.02/UU63

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH R01MH107512

**Title:** Direct brain recordings from children and adolescents reveal diverse patterns of PFC involvement in memory formation

**Authors: *E. L. JOHNSON**[1,2], Q. YIN[2], L. TANG[2], M. MALIK[2], E. ASANO[2,3], N. OFEN[2]
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**Abstract:** Human declarative memory improves remarkably across childhood and adolescence, concomitant with the maturation of the neocortex and widespread neocortical connectivity.

Prevailing functional MRI evidence points to the importance of protracted development of the prefrontal cortex (PFC) in the development of memory function. Until recently, however, it was not possible to detail the precise timing of PFC activity in the developing brain. We provide rare insight from individuals aged 5-17 (n = 12) undergoing direct cortical monitoring as part of clinical management (i.e., ECoG), which yields data with unprecedented spatiotemporal precision in the study of neurocognitive development. Subjects studied pictures of scenes, and judged whether each scene was indoors or outdoors in preparation for a recognition memory test. We analyzed task-evoked activity between 20-300 Hz to track PFC responses with millisecond precision during the encoding of scenes that were subsequently remembered. Importantly, activity in the gamma (>30 Hz) and high-frequency broadband (HFB; >70 Hz) ranges is correlated with the functional MRI BOLD response in humans, and HFB activity has been linked to neuronal spiking in the primate cortex. Spectral decomposition was performed using a multi-tapering approach with logarithmically spaced center frequencies and 1/3 fractional bandwidth, and 250-msec sliding time windows. Then, 3-sec encoding power segments were z-scored on the 300-msec pre-stimulus baseline (450-150 msec prior to scene onset) using a statistical bootstrapping procedure. We found that HFB increases in PFC were timed to the presentation and/or judgement of each scene, providing initial evidence that the developing PFC is involved immediately and dynamically during memory formation. These increases were observed in all subjects with single-trial reliability ($p < 0.05$) - with the most robust effects focused in middle frontal and precentral gyri, two regions that have been implicated in subsequent memory in adults. Furthermore, analysis of subsequently remembered versus forgotten scenes evidenced a partially overlapping and similarly diverse pattern of effects (all $p < 0.05$, permutation-corrected). We show that PFC exhibits spatially distributed, rapidly shifting, and behaviorally relevant patterns of activity during memory formation, even in young children. These findings provide novel evidence that challenges prevailing theories on the role of PFC in memory development.

**Disclosures:** **E.L. Johnson:** None. **Q. Yin:** None. **L. Tang:** None. **M. Malik:** None. **E. Asano:** None. **N. Ofen:** None.

**Poster**

**524. Cognitive Development**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 524.03/UU64

**Topic:** H.02. Human Cognition and Behavior

**Support:** Science of Learning Institute at Johns Hopkins University Award 80034917

**Title:** Visual cortices assume distinct cognitive functions in congenital and adult-onset blindness

**Authors: *R. PANT**[1], S. KANJLIA[1], C. LANE[2], M. BEDNY[2]
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**Abstract:** How does the potential for cortical plasticity change over the lifespan? In blindness, the visual cortices respond to somatosensory and auditory stimuli (Sadato et al., 1996, Nature; Collignon et al., 2011, PNAS). These responses are observed not only in congenital blindness, but also in adult-onset blindness (Collignon et al., 2013, Brain). Surprisingly, in congenitally blind individuals the visual cortices also become involved in higher-cognitive functions, such as language (Roder et al., 2002, European JoN.; Amedi et al., 2004, Nat Neuro; Bedny et al., 2011, PNAS). Do visual cortices also take on higher-cognitive functions in adult-onset blindness? More generally, do visual cortices perform similar cognitive functions in those who are blind from birth as opposed to those who become blind in adulthood?
In a previous study we showed visual cortices of congenitally blind people are more active during sentence processing than in a working memory control task with non-words. Furthermore, in congenitally blind but not sighted individuals, activity in the visual cortex increases with the grammatical complexity of sentences (Lane et al., 2015, JoN).
In the current study we used the same task to ask whether the visual cortices of adult-onset blind individuals show a similar or different functional profile. 18 congenitally blind, 11 adult blind (blindness onset after age 17) and 17 sighted participants were scanned while listening to sentences and performing a working memory task. Each sentence was followed by a yes/no question. Questions required participants to judge who did what to whom. Half the sentences were grammatically complex, i.e. contained syntactic movement. In the control task, participants decided whether the order of non-words in a probe stimulus matched the order of the same non-words in the target stimulus.
The visual cortex of adult-onset blind participants responded to sentences more than non-words when compared to the sighted participants, but this effect was much smaller than in the congenitally blind ($P < 0.05$). Unlike in the congenitally blind, the degree of response to sentences correlated with the duration of blindness in the visual cortex of the adult-onset blind ($r = 0.73$, $P < 0.05$), suggesting a different mechanism of plasticity. Crucially, unlike the visual cortex of the congenitally blind, the visual cortex of adult-onset blind participants did not respond to grammatical complexity (group-by-condition interaction $P < 0.05$). These findings suggest that visual cortices assume distinct cognitive functions in congenital and adult-onset blindness and suggest greater potential for functional repurposing of the cortex in childhood.

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**Poster**

**524. Cognitive Development**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 524.04/UU65

**Topic:** H.02. Human Cognition and Behavior

**Title:** Gene co-expression patterns underlie cognitive process divisions of human neocortex

**Authors: *D. R. SCHONHAUT**[1], A. E. KAHN[1], R. BETZEL[2], D. S. BASSETT[3]
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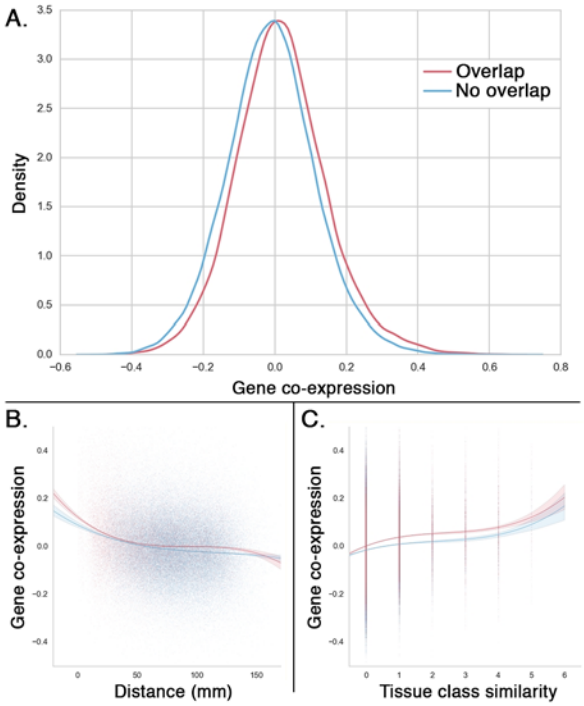
**Abstract: Background:**
Cortical regions participating in functional networks at rest exhibit highly correlated levels of gene expression. Yet, the relation between gene expression and cognition is unknown. We assessed whether correlated gene expression is elevated between regions engaged in similar task-related cognitive processes.
**Methods:**
Microarray data from postmortem tissue samples of 6 adults (Allen Institute Human Transcriptional Atlas) provided expression levels of 16,906 genes across 1,193 neocortical regions. Each region was assigned to 1 or more (of 12 total) cognitive processes, estimated from a hierarchical Bayesian model applied to 10,449 experimental contrasts in the BrainMap database. We assessed relations between gene co-expression (Pearson correlation across detrended expression levels) and cognitive process overlap (presence or absence of a shared cognitive process) among all cortical region pairs, while controlling for spatial proximity, tissue class similarity, and between-subject variance. Additionally, we performed enrichment analyses (GOrilla; $P<10e^{-4}$) on genes ranked by differential co-expression between regions with or without cognitive process overlap.
**Results:**
Overlapping cognitive processes characterized 29% of interregional connections. Gene co-expression was greater for connections with ($0.018 \pm 0.129$) versus without ($-0.009 \pm 0.125$) cognitive process overlap ($\chi^2=177.5$, $P<2.2e^{-16}$; **Fig. 1**). Genes that were preferentially co-expressed between regions with cognitive process overlap were enriched for 40 cell component and 94 biological process terms relating largely to activity and maintenance of synapses. In contrast, no gene ontology term was enriched among genes preferentially co-expressed between regions without cognitive process overlap.
**Conclusion:**
Gene co-expression is elevated between regions engaged in similar cognitive processes, due in part to coupled expression of genes involved in synaptic communication. This result suggests a molecular basis for the organization of human neocortex into task-related networks.

Figure 1. Co-expression between regions with and without cognitive process overlap.




**Disclosures:** **D.R. Schonhaut:** None. **A.E. Kahn:** None. **R. Betzel:** None. **D.S. Bassett:** None.

**Poster**

**524. Cognitive Development**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 524.05/UU66

**Topic:** H.02. Human Cognition and Behavior

**Support:** Autism Speaks 7608

Department of Defense AR130106

Leon Levy Foundation

**Title:** Statistical learning is associated with autism symptoms and verbal abilities in young children with autism

**Authors: *R. M. JONES**[1], T. TARPEY[2], A. HAMO[1], C. CARBERRY[1], G. J. BROUWER[3], C. LORD[1]

[1]Psychiatry, Weill Cornell Med., White Plains, NY; [2]Wright State Univ., Dayton, OH; [3]Dept. of Psychology and Ctr. for Neural Sci., New York Univ., New York, NY

**Abstract:** Statistical learning, the ability to extract regularities in our environment, may be fundamental for social behavior. We tested 124 young children (ages 2-8 years), 56 children with autism compared to 68 typically developing children on a novel, flexible visual statistical learning task to determine whether individual variability in statistical learning was associated with autism symptoms. On average, as a group, children with autism appeared to demonstrate no learning on the task compared to typically developing children. However, Bayes classification probabilities, which measured how likely an individual child's pattern of learning was similar to that of a typically developing child, demonstrated that there was significant overlap in learning patterns between a subset of children with autism and typically developing children. Children with autism who demonstrated clear learning on the task had less severe autism symptoms. Children with autism and typically developing children with higher verbal abilities demonstrated superior statistical learning abilities. Together, findings suggest that averaging data in young children with autism may mask heterogeneity. Individual variability in statistical learning may help to understand differences in symptoms across individuals with autism. The results have significant clinical implications for identifying distinct learning patterns in young children with autism that could be used to tailor and inform treatment decisions. Behavioral findings will be the foundation for future research during functional Magnetic Resonance Imaging to understand the neural underpinnings of individual variability in statistical learning in autism.

**Disclosures: R.M. Jones:** None. **T. Tarpey:** None. **A. Hamo:** None. **C. Carberry:** None. **G.J. Brouwer:** None. **C. Lord:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Lord receives royalties from Western Psychological Services (WPS) for the ADOS and ADI-R..

**Poster**

**524. Cognitive Development**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 524.06/UU67

**Topic:** H.02. Human Cognition and Behavior

**Title:** Cognitive control training supports the functional integration of control networks in adolescence

**Authors: R. LEE**[1], S. KWAK[2], D. LEE[2], *J. CHEY[2,1]
[1]Interdisciplinary Program in Brain Sci., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Psychology, Seoul Natl. Univ., Seoul, Korea, Republic of

**Abstract:** Cognitive control continues to mature throughout adolescence, and lower cognitive control at this time is linked to various clinical outcomes such as risk-taking behavior, substance abuse, and mental disorders. Although some research examined behavioral effects of cognitive control training in adolescents, no studies have explored the neural basis of these training effects. In this study, we investigated resting-state connectivity (rsFC) using functional magnetic resonance imaging (fMRI) before and after 6 weeks of cognitive control training in 51 adolescents (mean age 13.2 years). A seed-based functional connectivity analysis was conducted, with the seed regions identified through an automated meta-analysis to be implicated in cognitive control. The trained group showed increased rsFC between right anterior insula/frontal operculum (aI/FO) and cerebellum compared with the control group. This result can be interpreted in the context of developmental change, which implies that the development of positive functional connections between cerebellar network and other cognitive control networks in adolescence was promoted by cognitive control training. In other words, given that previously isolated regions of the cerebellar network have been reported to coalesce into two other control networks (fronto-parietal and cingulo-opercular networks) at this age, our result suggests this functional integration of control networks over development was accelerated by intensive training. Using well-established cognitive control networks as regions of interest (ROIs), a follow-up analysis revealed that rsFC between cingulo-opercular and cerebellar networks was strengthened in the trained group compared with the control group. Furthermore, increased strength of connectivity was associated with improvement in Block Design test, with the magnitude of these connectivity changes being reflected by individual gains in cognitive control performance. These findings emphasize the supportive role of cognitive control training in enhancing functional integration of control networks that may drive cognitive control improvement in adolescence.

**Disclosures:** **R. Lee:** None. **S. Kwak:** None. **D. Lee:** None. **J. Chey:** None.

**Poster**

**524. Cognitive Development**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 524.07/UU68

**Topic:** H.02. Human Cognition and Behavior

**Title:** Mvpa exploration of autism networks

**Authors: *D. P. PANFILI**[1], K. Z. OSIPOWICZ[2]
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**Abstract:** Autism spectrum disorder (ASD) is a common but heterogeneous spectrum of developmental disorders. The nociferous effects of ASD have been demonstrated on cognitive, functional, and structural levels. All of these previous studies support the view that ASD is a

network disease, affecting function and structure of cortical and subcortical regions throughout the brain. Though all of these effects are well established, previous investigations into network disruption caused by ASD have been hypothesis driven. Hypothesis driven analyses of network effects are insightful, but limited in that they do not allow untethered exploration of network disruption. Here, we analyzed network differences between 531 ASD patients and 571 age matched controls utilizing a support vector machine multi-voxel pattern analysis of resting state functional connectivity data. Additionally, utilizing a similar analytic approach, we analyzed network disruptions occurring differentially between ASD severity, as determined by ASD DSM-V severity level and ADOS score. Our findings confirm that ASD causes wide ranging network disruptions, and that functional connectivity evidence of these disruptions is a distinguishing feature of ASD, and that there are a number of distinguishing features of severity level classification. These findings confirm and replicate a number of previous effects, and extend the understanding of ASD as a network disorder affecting multiple functional domains.

**Disclosures: D.P. Panfili:** None. **K.Z. Osipowicz:** None.

**Poster**

**524. Cognitive Development**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 524.08/UU69

**Topic:** H.02. Human Cognition and Behavior

**Title:** fMRI with awake, behaving infants: Theoretical impact

**Authors: *C. T. ELLIS**[1,2], L. J. SKALABAN[1,2], N. I. CORDOVA[2], V. R. BEJJANKI[2,3], N. B. TURK-BROWNE[1,2]
[1]Yale Univ., New Haven, CT; [2]Princeton Univ., Princeton, NJ; [3]Hamilton Col., Clinton, NY

**Abstract:** Much of what we know about learning and memory in the human brain comes from adults. However, the greatest period of learning in life happens early in development as infants and toddlers acquire language, gain knowledge about the world, build motor and social skills, etc. This poses a challenge for theories of learning and memory because many of the brain systems involved in adults may not be fully functional in infancy. For example, complementary learning systems theory posits that the medial temporal lobe (more specifically, the hippocampus) is needed to represent individual episodes in memory. However, the hippocampus has a protracted developmental trajectory, with critical subregions only coming online after infancy and possibly not until adolescence. Thus, episodic memory in infants may be implemented in a different way. Likewise, an updated version of the same theory posits that the hippocampus is also needed for statistical learning, our ability to extract regularities across episodes, and yet there is considerable behavioral evidence of statistical learning in infants and even newborns. These tensions highlight the critical need for more data on brain function in

awake, behaving infants. The most common neuroscience methods for this population, such as EEG and NIRS, are surface based and thus cannot resolve deep structures like the hippocampus. Therefore we have been exploring the viability of conducting fMRI studies in infants and toddlers while they perform tasks designed to test episodic memory and statistical learning. Here we will present initial findings from these investigations as well as broader considerations associated with studying learning and memory in early development. One possible outcome is that the hippocampus is not involved in either episodic memory or statistical learning at this age. Alternatively, the hippocampus may be at least partly functional early on and already supportive of both behaviors, as in adults. Finally, a middle ground is that episodic memory and statistical learning may depend on different pathways within the hippocampus that develop at different rates, thus hippocampal activation may emerge earlier in one task than the other. Specifically, statistical learning is supported by the monosynaptic pathway to CA1, which develops earlier in non-human primates than the trisynaptic pathway, which passes through dentate gyrus and CA3, and supports episodic memory. Findings from these studies will help reveal the organization of the developing mind and inform existing theories about mechanisms in the brain that are critical for learning and memory.

**Disclosures: C.T. Ellis:** None. **L.J. Skalaban:** None. **N.I. Cordova:** None. **V.R. Bejjanki:** None. **N.B. Turk-Browne:** None.

**Poster**

**524. Cognitive Development**

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**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 524.09/UU70

**Topic:** H.02. Human Cognition and Behavior

**Title:** fMRI with awake, behaving infants: Methodological considerations

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**Abstract:** There have been thousands of fMRI studies over the past two decades, and they have provided important insights about how the adult mind and brain work. In light of this success, it is striking that only a small handful of fMRI studies have tested infants in the same way. This is not for a lack of interesting and deep questions about cognitive development — indeed, such a rich dependent measure could open up exciting new questions and opportunities for studying preverbal infants. Rather, the dearth of studies likely reflects the technical and experimental challenges of conducting fMRI studies in this population, including head motion, attention span and fussiness, an ability to understand or follow instructions, acoustic noise, a scanning

apparatus that is typically designed for adults, and analyses optimized for adult data. Some labs have successfully scanned infants, particularly when they are sleeping or sedated, but there have been few attempts to translate paradigms from infant cognition to the scanning environment. Here we report on our efforts over the past two years to re-imagine task-based fMRI procedures for early development. Our approach has benefitted from recent progress in cognitive neuroscience in the acquisition and analysis of adult fMRI data, and from the methodological and theoretical groundwork laid by developmental psychologists. We have devised several novel procedures that increase the likelihood of successfully scanning awake, behaving infants, maximizing the amount of useful brain data collected per session, while also collecting behavioral eye-tracking data. First, we changed the scanning environment to increase infant comfort, including using vacuum pillows to reduce movement, supplying redundant hearing protection, and involving parents in the scans. Second, we altered experimental designs and equipment, including presenting stimuli panoramically on the ceiling of the scanner bore, importing successful stimuli and tasks from the infant cognition literature, and building flexible code for running experiments in short modules. Third, we composed a novel analysis pipeline that incorporates cutting-edge tools from several packages to assess data quality, identify and scrub motion artifacts, and, when possible, functionally align brains longitudinally within participant and cross-sectionally across participants. With these procedures, we have thus far obtained usable data from 11 out of 15 participants under the age of 18 months. Although this endeavor continues to be challenging, our hope is that these methodological insights will eventually increase the prevalence of early developmental fMRI.

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**Poster**

**524. Cognitive Development**

**Location:** Halls A-C

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**Program#/Poster#:** 524.10/UU71

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**Title:** Local functional connectivity development in early childhood: Associations with socioeconomic status

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**Abstract:** Over the course of development, children undergo large changes in functional brain organization, and these changes have been shown to be sensitive to early experiences.

Many studies have characterized developmental changes in the resting state functional connectivity of specific brain structures and networks. However, no studies have investigated changes in patterns of local connectivity across the brain in early childhood. Regional homogeneity (ReHo) is an analytical approach that compares each voxel's blood oxygen time course at rest to its neighboring voxels. In adults, ReHo is highest in sensory regions and the default mode network (Lopez-Larson et al., 2011), a result that is consistent with high local connectivity in these regions (Sepulcre et al., 2010).
In this study, we conducted whole-brain ReHo analyses in a sample of children ages 3-10 from the Pediatric Imaging Neurocognition and Genetics (PING) dataset ($n$=64). All analyses controlled for motion, site of data acquisition, and sex, and were corrected for multiple comparisons using permutation testing (FSL's randomise) at $p < .05$. We found that ReHo was highest in sensory and motor cortices. ReHo decreased with age in sensory and motor cortices and in subcortical structures. ReHo increased with age in regions of the default mode network (as defined by Yeo et al., 2011), including posterior cingulate, precuneus, and left inferior frontal gyrus (IFG). Additionally, there was a positive correlation between socioeconomic status (SES), and ReHo in an area of right IFG at the intersection of three networks: default mode, frontoparietal, and ventral attention.
In sum, we found that, as in adults, sensory and motor cortices have relatively high local connectivity, and that local connectivity decreases with age in these regions. In contrast, default mode areas show increases in local connectivity with age. Further, our findings suggest that SES may have an impact on the development of local connectivity at the junction of networks in prefrontal cortex. Future analyses will examine the associations between the development of local connectivity, SES, and cognition.

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**Poster**

**524. Cognitive Development**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NICHD grant P50 HD052117

**Title:** Task control network brain activity before intervention relates to future reading gain in struggling readers

**Authors: *T. NUGIEL**[1], M. ROE[1], W. TAYLOR[2], J. M. FLETCHER[2], J. J. JURANEK[3], J. A. CHURCH[1]
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**Abstract:** Reading is a fundamental life skill, but many children have reading difficulties, with nearly one in three children reading below a basic level in 4th grade (NEAP, 2015). Responses to reading interventions can vary and behavioral measures cannot always predict whether a struggling reader will respond to a given intervention. At the same time, the role of task control processes in reading provides an important less-explored angle on reading development. This study tested for brain activity differences in reading and control regions both within a group of struggling readers and between struggling and typical readers based on whether the struggling readers went on to show substantial reading gains at the end of the school year.
We used functional magnetic resonance imaging (fMRI) data in 4th grade children to measure activity in reading and task control regions of interest (ROIs) related to reading outcomes. 46 struggling readers (26 males) and 31 age-matched typical readers (15 males) performed an in-scanner sentence comprehension task as well as an out-of-scanner battery of neuropsychological and reading measures. Struggling readers also repeated both in and out of scanner measures in the spring after remedial instruction. Whole brain analyses for the correct response > baseline contrast and the mean percent signal change extracted from literature-derived ROIs were used to test for reader group differences. Gains in reading measures calculated from pre-post (fall-spring) test score changes were used to sort struggling readers at the pre-intervention scan (fall) into future improver and future non-improver groups. Importantly, there were no differences in reading ability or IQ between future improvers and future non-improvers before instruction (all *p's* >0.10).
We saw whole brain differences in activation between future improvers and future non-improvers in bilateral ventral fusiform, as well as ROI differences in a right frontal task control region ($t(34.92) = 2.28$, $p = 0.03$). Differences in activation between future improvers and typical readers were seen in task control and default network regions at the whole brain level, as well as in left inferior parietal ($t(50.27) = -2.05$, $p = 0.04$) and left inferior frontal gyrus ($t(46.23) = 2.06$, $p = 0.04$) ROIs. Taken together, these findings suggest that recruitment of task control brain regions, in addition to reading regions, may be important predecessors for subsequent reading gain in 4th grade struggling readers.

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**Title:** Higher responsiveness to familiar scenes in the retrosplenial cortex develops in late childhood

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**Abstract:** *Introduction:* Our ability to recognize a current visual scene as familiar or unfamiliar is a key necessity for a good sense of orientation and enables us to successfully navigate our environment. Younger children (< 10 years) display a notably lower proficiency in recognizing scenes as familiar vs. unfamiliar, while older children (10-12 years) perform as well as adults. An underdeveloped functioning of the visual cortical scene processing network (parahippocampal place area (PPA), retrosplenial cortex (RSC), transverse occipital sulcus (TOS, also named occipital place area, OPA)) in younger children might be an underlying factor for their lower capability to efficiently recognize scenes as familiar or unfamiliar. Studies in adults suggest that especially the RSC is highly responsive to the familiarity of scenes, while a familiarity effect in the PPA and the TOS is rather unreliable. So far, studies on the functional development of the scene processing network almost exclusively focused on the PPA. Moreover, the emergence of a responsiveness towards familiarity has not been investigated in pediatric samples. *Method:* Here, we investigated the development of the scene processing network's response to familiar scenes in contrast to new scenes. We analyzed BOLD amplitudes with regard to stimulus category (familiar scene, unfamiliar scene) in three age groups (7-8-year-olds, 11-12-year-olds, adults) in a mixed ANOVA for scene-selective regions (PPA, RSC, TOS, subject-specifically defined using a separate scene localizer). *Results:* Preliminary analysis of 27 participants so far reveled a higher response to familiar vs. unfamiliar scenes in all regions of interest across age groups. Moreover, our results suggest an RSC-specific development of familiarity responsiveness in late childhood: Both younger and older children did barely differ between responses to familiar vs. unfamiliar scenes. In comparison, adults developed a larger response to familiar scenes while their response to unfamiliar scenes stayed constant. We found the same pattern for the rRSC, albeit as a nonsignificant trend. Familiarity x age group interactions were not evident in PPA or TOS. *Discussion:* These results indicate that while the behavioral development of scene recognition in concluded early (up to age 12), functionality in the scene-selective RSC continues to develop beyond the age of 12 years of in terms of a familiarity effect. This provides evidence for further neuronal maturation processes in the scene network that do not have a behaviorally measurable equivalent in navigation or sense of orientation tasks.

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**Title:** A sensitive period for higher-cognitive repurposing of visual cortex in blindness

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**Abstract:** Recent evidence suggests that visual cortices not only respond to auditory and somatosensory input, but are repurposed for higher cognitive functions, such as language and mathematical reasoning in congenital blindness (Kanjlia et al., 2016, PNAS). In addition, resting-state activity of visual cortices becomes more correlated with fronto-parietal networks (Deen, et al., 2015, JoCN). Is such dramatic functional reorganization restricted to a sensitive period early in development? To address this question, we compared visual cortex function and connectivity across congenitally blind, adult-onset blind and sighted individuals.
While undergoing fMRI, 12 adult-onset blind (AB; vision loss after age 17), 20 congenitally blind (CB) and 19 blind-folded sighted adults performed an auditory math task in which they decided whether the value of an unknown variable across two math equations was the same. Math equation difficulty was manipulated by increasing digit-number (e.g. 7-2=x vs. 27-12=x) and by moving the x variable (e.g. 7-2=x vs. x-2=7). In a language control task, participants decided if pairs of sentences had the same meaning. Participants (11 AB, 23 CB, 38 S) took part in 1-4 8-minute resting state scans to evaluate visual cortex functional connectivity with fronto-parietal language and number networks.
All groups recruited a classic fronto-parietal number network, including the intraparietal sulcus, during the math task. However, unlike congenitally blind individuals, adult-onset blind individuals did not recruit visual cortices selectively during the math task (whole-cortex, math>lang, $p<0.05$, cluster-correct.). Although visual cortices of adult-onset blind individuals demonstrated an indiscriminately larger response to auditory stimuli compared to sighted individuals, activity was not modulated by task (math vs. lang) or by equation difficulty, as observed in congenitally blind individuals (digit-number by group (CB vs. LB) interaction: $F(1,30)=4.11$, $p=0.05$). Thus, a subset of visual regions only assumes mathematical functions in congenital blindness. Interestingly, resting state data revealed an intermediate connectivity pattern in the adult-onset blind group, relative to the sighted and congenitally blind participants. Similar to the congenitally blind group, the adult-onset blind group showed network-specific

increases in resting-state functional connectivity between visual and prefrontal cortices. These results suggest that changes in functional connectivity in blindness lead to visual cortex plasticity for higher cognitive functions, but only during a sensitive period early in development.

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**Poster**

**524. Cognitive Development**

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**Title:** White matter integrity is related to cognitive ability in early life

**Authors:** ***J. N. BULLINS**[1], E. CORNEA[1], B. D. GOLDMAN[2], R. C. KNICKMEYER[1], M. STYNER[1,3], J. H. GILMORE[1]
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**Abstract: Background:** Mounting evidence reveals white matter (WM) integrity as an indicator of cognitive ability in children and adults. However, it is unknown how WM fibers support cognitive development in early life. This study explores relationships between *in-vivo* WM microstructural properties and cognitive ability in the first 2 years of life.
**Methods:** Tract-based diffusion properties (FA, RD, AD) were computed using diffusion tensor images from healthy neonates (n=332), 1-year-olds (n=255), and 2-year-olds (n = 181). Cognitive measures at ages 1 and 2 (ELC1, ELC2) were collected using the Mullen Scales of Early Learning. Data were analyzed using raw and partial correlations and mixed effects models comparing global tract-average properties at birth, age 1, and age 2 to ELC1 and ELC2. All results were corrected for multiple comparisons using false discovery rate (FDR).
**Results:** Unadjusted Pearson's correlations revealed widespread significant correlations between individual tract FA ($0.13 \leq r \leq 0.22$; $p<0.05$), AD ($-0.23 \leq r \leq -0.13$; $p<0.05$), RD ($-0.25 \leq r \leq -0.14$; $p <0.02$) and ELC2. However, FA, RD, and AD are significantly correlated with

gestational age at birth (FA: $0.11 \leq r \leq 0.44$, $p < 0.003$; AD: $-0.48 \leq r \leq -0.29$, $p < 0.0001$; RD: $-0.49 \leq r \leq -0.31$, $p < 0.0001$) and gestation number (FA: $-0.30 \leq r \leq -0.12$, $p < 0.004$; AD: $0.22 \leq r \leq 0.39$, $p \leq 0.0002$; RD: $0.24 \leq r \leq 0.38$, $p < 0.0001$), and controlling for these covariates in partial correlations revealed no significant relationships between WM at birth and ELC2. Gestational age ($r = 0.34$, $p < 0.0001$), gestation number ($r = -0.35$, $p < 0.0001$), and maternal education ($r = 0.41$, $p < 0.0001$) were also directly related to ELC2; these factors were not related to ELC1. At age 1, widespread correlations were found between tract RD, AD and ELC1, mainly in projection tracts from the brainstem and thalamus to cortex, and also in arcuate and superior longitudinal fasciculi (SLF; all results: $-0.21 \leq r \leq -0.14$, $p < 0.05$). The left SLF at age 2 was related to ELC2 ($p<0.05$); no other brain-cognition relationships at this age survived FDR. **Conclusions:** More mature microstructural properties along WM bundles at birth and 1-year is related to future and present cognitive ability. WM integrity at birth is related to gestational characteristics, and these gestational characteristics along with maternal education are important sociodemographic predictors of cognition at age 2. Tracts detected as markers of early ability are important for primary sensory, sensory integration, and higher-order cognitive functions. Results suggest WM integrity in early life, particularly across the first postnatal year, is important for emerging cognition and deserves further study.

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**Poster**

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**Title:** Dorsal visual network connectivity develops earlier than ventral as reflected in cortical thickness and task-related ERPs

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**Abstract: Introduction:** We present converging evidence from MRI cortical morphometry and ERPs studies that a pattern of connectivity of cortical nodes within two attentional networks - the *Dorsal Visual Network* (**DVN**; visual-spatial w. frontal dorsal-parietal nodes) and *Ventral Visual Network* (**VVN**; object categorization w. frontal ventral-temporal nodes) demonstrates an earlier track of maturation for DVN than VVN. **Methods:** Thirty typically developing children rigorously selected using neuropsychological tests (**TD**; age 6-15) and thirty young adults (**A.;** 21-40) participated in studies. 3D MRI scans were used to construct individual cortical surfaces yielding a gray/white matter/pial boundry model. MRI Cortical Thickness (**CTh**) was mapped to the inflated surface. The development of *structural connectivity* was defined as the age-dependent thinning of the cortex, where two cortical nodes, highly connected, showed a significant pair-wise correlative relationship (significant network edge). Stop-Response Task-related Event-Related Potentials (ERPs) were analyzed. The ERPs cortical *functional connectivity*, as measured by P200-N200 peak amplitude and latency in frontal and posterior nodes, respectively, were submitted to correlative analysis within the DVN and VVN cortical nodes. **Results:** Between-group contrasts t-statistics (Cohen's D) and within-group Pearson's r for linear relationship between variables (N200, P200 amplitudes, latencies) showed no significant differences TD vs. A for DVN in cortical thickness (except Frontal Premotor) and in ERPs amplitude or latency measures. The correlative computations showed significantly less connectivity between long-range nodes in TD than A, for both CTh and ERPs P200/N200 amplitudes, with a statistically significant group discrepancy for measures in VVN. The peak latency was persistently prolonged in TD. Long-range VVN network frontal-temporal nodes connectivity, displayed in A was significantly lower or nonexistent in young TD children (e.g. prefrontal ventral to fusiform gyrus). **Conclusion:** The MRI CTh morphometry and ERPs P200/N200 reflect a tight cohesiveness in displaying less child-adult differences in structural and functional connectivity between nodes of the DVN but more statistically significant group differences for VVN, thus suggesting an earlier maturational course for DVN. This finding, consistent with a proposed earlier hypothesis of specific DVN susceptibility to pathology in disorders of early childhood (Atkinson et al., 1999; Braddick et al., 2011), is of high importance for early clinical diagnosis and prevention, and for understanding chronometry of typical development.

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**Poster**

**524. Cognitive Development**

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**Topic:** H.02. Human Cognition and Behavior

**Title:** Early educational intervention for poor children modifies brain structure in adulthood

**Authors: *M. J. FARAH**[1], J. T. DUDA[2], T. A. NICHOLS[3], S. L. RAMEY[4], P. R. MONTAGUE[5], T. M. LOHRENZ[4], C. T. RAMEY[4]
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**Abstract:** The Abecedarian project was an experimental early childhood intervention for poor children, which provided comprehensive cognitive and social enrichment in a daycare setting for 6–8 hours a day, five days a week, starting in infancy and continuing through age 5. Activities emphasized language and play-based learning. A control group received nutritional support, health care, and social services, as did the intervention group, so that outcome differences would not be attributable to these factors. Over the ensuing decades participants were evaluated on their functioning in various important spheres of life including educational, occupational, economic, and health outcomes, with significant positive impacts of the intervention apparent by several measures. Now in their late 30's and early 40's, the participants were imaged with MRI of the brain to examine whether those who experienced an enriched early education had measurable differences in brain structure. Forty-seven participants could be successfully scanned; 29 of these (15 males, 14 females) were in the early educational intervention group and 18 (9 males, 9 females) were in the control group. Covarying sex and age, initial findings were (here and throughout, standardized regression coefficients and 2-tailed significance levels): Larger overall cortical grey volume ($\beta$=.23, p=0.035) and borderline significant larger white matter volume ($\beta$=.21, p=0.084), with no difference in overall deep grey matter volume. Five a priori regions of interest were selected to assess the effects of the intervention on areas related to language (L inferior frontal gyrus, L superior temporal gyrus) and cognitive control (L and R anterior cingulate cortex and R inferior frontal gyrus) covarying whole brain volume as well as the earlier covariates. Of these 5 regions, two showed significant positive effects of intervention, L IFG ($\beta$=.38, p=0.005) and R IFG ($\beta$=.37, p=0.006) and one showed a borderline significant effect, L ACC ($\beta$=.27, p=0.08). In sum, children from poor families who experienced an intensive language and play-based educational intervention starting early in life had more cortical grey matter and, in a preliminary examination of specific regions, larger IFG volumes bilaterally in middle adulthood.

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**Poster**

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**Title:** Neural and behavioral development of visual-spatial construction ability

**Authors: *K. FERRARA**[1], A. SEYDELL-GREENWALD[1], C. E. CHAMBERS[1], E. L. NEWPORT[1], B. LANDAU[1,2]
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**Abstract:** Spatial representations underlie many cognitive tasks, including memory for spatial configurations and mental rotation. The literature has tended to attribute spatial abilities to the right hemisphere (RH) parietal areas of the brain, but even the classic task of mental rotation appears to activate bilateral parietal regions. Recently, we adapted a widely used visual-spatial construction task to examine neural patterns in adults, and found strong bilateral activation. In the present research, we ask whether this is also shown in young children, or alternatively, whether a pattern of RH lateralization precedes the mature pattern of bilateral activation.
fMRI activity was measured in typically developing children ages 5–11 years (n = 22, mean age = 8.03 years) while they performed a visual-spatial construction task. The task engages several aspects of spatial ability, including representation of object shape and orientation as well as mental translation and rotation. In the Spatial condition, participants indicated whether two separated puzzle pieces could be fit together to form a square. In the Color (control) condition they indicated whether gray squares on the pieces were the same color.
Children obtained high levels of task accuracy ($M$ = 90%, $SD$ = 9%), which was positively correlated with age. Analyses of neural activity at the individual level showed significant clusters of activation in bilateral superior and inferior parietal areas of all participants (Spatial > Control condition, $p < .001$, $k < .05$). The number of active voxels was positively correlated with age, with older children showing a greater number of significantly active voxels. Hierarchical linear regression confirmed that this relationship remained unchanged when controlling for accuracy. This age-related increase in spatial extent (number of voxels) reflects the expanding involvement of parietal regions.
No correlations were found among the variables of response time, IQ (WASI-II), or motion parameters. Functional cluster parietal ROIs were defined by a GLM (contiguous supra-threshold voxels) and BOLD response amplitudes of these ROIs were calculated. These did not show a

correlation with either age or number of active voxels. There were no differences between the RH and LH in terms of either voxel counts or response amplitudes. This reveals a strong and consistent bilateral activation pattern. Across development and into adulthood, both the RH and LH contribute to the complex computations underlying visual-spatial construction.

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**524. Cognitive Development**

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**Program#/Poster#:** 524.18/UU79

**Topic:** H.02. Human Cognition and Behavior

**Title:** Adolescents are sensitive to peer influence, but only for so long

**Authors: *J. M. RODRIGUEZ BURITICA**[1], H. R. HEEKEREN[2], W. VAN DEN BOS[3]
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**Abstract:** Adolescents have the reputation to be fickle and easily influenced by their peers, particularly to do things that may not be in their best interest. Indeed several studies have shown that specifically teenagers show increased levels of risk taking in the presence of peers (Albert et al., 2013). Yet a recent study also suggest that adolescents, compared to adults, may be less influenced by prior instructions and put relative more weight on their own experience (Decker et al., 2015). Thus at this point it is not clear how these findings can be resolved and whether adolescents are more sensitive to prior social advice, particularly of their own peers, or weight their own experience more heavily. Here we present an age-comparative study (in 8-10, 13-15 and 18-22 year olds) study that investigates the mechanisms of learning from social and individual information. Using computational models we are able to test the interaction between different (social) learning mechanisms, and track how they change with age. Our results suggest that there are two mechanisms that facilitate social learning: 1) setting initial expectations (priors) and 2) a constant bonus for the advised option. More importantly, our results show that adolescents are indeed initially the most sensitive to their peer's advice (sets a strong prior), but that this is quickly updated by their own experience. On the other hand, adults show the long lasting bias towards the advised option. Finally, we also find that the younger participants are in general more exploratory, and this helps adolescents even to find out more advantageous information. Our results provide novel insights in the dynamic interaction between social and individual learning and also provide a framework for understanding previous (seemingly conflicting) results.

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**Poster**

**525. Human Motor and Sequence Learning**

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**Title:** Casual prefrontal cortex neuromodulation of reinforced skill learning

**Authors: *J. HERSZAGE**[1], E. DAYAN[2], R. LAOR MAAYANY[1], N. CENSOR[1]
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**Abstract:** Procedural motor skill learning is mediated by reinforcement, whether in the form of reward or by punishment (Abe et al., 2011; Dayan et al., 2014b; Galea et al., 2015). However, a mechanistic account identifying the neural substrates underlying reward based motor skill learning is incomplete. The lateral prefrontal cortex (lPFC) is densely connected with motor (Cieslik et al., 2012; Hasan et al., 2013), declarative/hippocampal (Preston and Eichenbaum, 2013) and reward systems (Haber, 2011; Jarbo and Verstynen, 2015). We thus hypothesized that due to the system interactions of lPFC with procedural, declarative and reward networks, it plays a crucial role in reinforcement-based skill learning and memory formation. To explore the causal role of the human lPFC in reinforced skill learning, participants (n=20) in the current study performed the motor skill learning task (Karni et al., 1995), in a rewarded or non-rewarded paradigm, after undergoing non-invasive brain stimulation (TMS). Baseline performance levels were comparable between the two counterbalanced sessions ($t_{19}$=1.836, ns). In comparison to control vertex stimulation, inhibitory 1Hz rTMS over the lPFC diminished learning gains, relative to baseline performance ($F_{1,19}$=4.57, $p<0.05$). In addition, correlation between task-free functional connectivity of distinct memory systems and the behavioral motor skill formation, are measured. The results reveal a unique role for the lPFC underlying reinforced acquisition of complex skills, and may suggest that it mediates systems-wide interactions across memory and reward networks.
* Eran Dayan and Jasmine Herszage contributed equally to this work

**Disclosures:** **J. Herszage:** None. **E. Dayan:** None. **R. Laor Maayany:** None. **N. Censor:** None.

**Poster**

**525. Human Motor and Sequence Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 525.02/UU81

**Topic:** H.02. Human Cognition and Behavior

**Support:** FWO Grant G099516N

**Title:** Enhancing cortical targeting for non-invasive brain stimulation in order to modulate the consolidation of motor sequence memory

**Authors: *M. A. GANN**[1], B. R. KING[1], D. MANTINI[1], M. DAVARE[1], S. SWINNEN[1], E. M. ROBERTSON[2], G. ALBOUY[1]
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**Abstract:** Motor sequence memory consolidation is supported by dynamical interaction between striato- and hippocampo-cortical networks (Albouy et al., 2013). However, it remains unknown whether activity within these networks can be modulated in order to influence the consolidation process. The aim of the present study is to use resting-state (RS) functional connectivity to identify potential cortical areas that can be subsequently targeted with non-invasive brain stimulation (NIBS) in order to modulate the interaction between these two brain networks, ultimately influencing motor memory consolidation.
RS fMRI data were recorded on 26 young healthy subjects (mean age: 25.4 y.o.) with EPI sequences (TR=2.5s, voxel size=2.5x2.5x2.5mm$^3$) in a 3T MRI scanner. Whole-brain functional RS connectivity maps using the hippocampus and the caudate nucleus as seeds (defined anatomically bilaterally according to the AAL brain atlas) were computed with procedures similar to Solesio-Jofre et al. (2014). Conjunction analyses between the resulting hippocampal and striatal RS connectivity maps were performed in order to identify cortical nodes connected to both seed regions. Results indicate that the left DLPFC (-26 18 52mm) was significantly commonly connected to the hippocampus ($z$=2.30, $p_{FDR}$<.05) and the caudate nucleus ($z$=2.44, $p_{FDR}$<.05). Additional clusters in the conjunction map were also present in midline default mode network regions (e.g., MPFC, cingulum) as well as in the cerebellum and thalamus. In order to confirm that the identified DLPFC region is relevant for motor sequence learning, we analyzed an independent sample of task-related fMRI data obtained from 55 young healthy participants (mean age: 23 y.o.) with EPI sequences (TR=2.65s, voxel size=3.4x3.4x3 mm$^3$) in a 3T scanner. Whole-brain Psycho-Physiological Interaction analyses were conducted using the above-mentioned left DLPFC as a seed region. Results indicate that task-related functional connectivity between the DLPFC and the left parahippocampus (-32 -46 -12mm, $z$=3.54, $p_{FWEsvc}$<.05) as well as the left putamen (-28 -10 -6mm, $z$=3.38, $p_{FWEsvc}$<.05) was modulated by performance on the

motor task.
Altogether, our results suggest that the DLPFC is a critical cortical node orchestrating functional interactions between hippocampal and striatal networks involved in motor memory processes. Future research will use the identified DLPFC cluster as a cortical target for NIBS in order to modulate activity in the hippocampal and striatal networks and ultimately influence motor memory consolidation.

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**Poster**

**525. Human Motor and Sequence Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

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**Topic:** H.02. Human Cognition and Behavior

**Support:** CIHR

NSERC

**Title:** The evolution of whole-brain community structure during sensorimotor adaptation

**Authors: *D. STANDAGE**, J. Y. NASHED, J. R. FLANAGAN, J. P. GALLIVAN
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**Abstract:** Traditionally, sensorimotor adaptation was believed to be solely driven by an implicit learning process, characterized by a slow, automated reduction in sensory prediction errors. However, recent behavioral evidence suggests that explicit cognitive strategies also play an important role in adaptation, supporting faster learning and re-learning when encountering the task a second time (savings). While previous behavioral work has proven invaluable in characterizing the distinct computations supporting sensorimotor learning, its underlying neural bases remain poorly understood. To date, neural studies of adaptation learning have largely focused on changes in the activity of single brain regions or the interactions between several such regions, failing to fully capture the widely accepted notion that learning reflects a whole-brain process, involving the coordination of brain regions over a broad range of spatial and temporal scales. Moreover, it remains unclear which features of functional brain network organization underlie well known differences across participants in their capacities for learning and their expression of savings. Here, we used functional magnetic resonance imaging (fMRI) to investigate the whole-brain, large-scale temporal networks that govern visuomotor rotation learning and re-learning. Participants performed two separate MRI sessions, separated by 24 hours. On each trial, they moved a centrally located virtual cursor, via the hand, to contact one of

eight possible targets. On each testing day, following baseline trials, we introduced an instantaneous 45 degree rotation of the hand cursor with respect to the hand and tracked participant learning during continuous MRI acquisition. Following earlier studies (Bassett et al, PNAS, 2011; Bassett et al, Nat Neurosci, 2015), we used time-resolved clustering methods to determine the community structure of multi-layer networks collated across sliding time windows during rotation learning on each day. We quantified the modularity of network structure, the extent to which brain regions changed community affiliation, and the probability that any two brain regions were assigned to the same community. We show that participants who exhibit the behavioral signatures of explicit, cognitive strategies during learning also exhibit greater flexibility in their network community structure, particularly in frontal and ventrotemporal brain areas. Our results suggest that individual differences in sensorimotor adaptation are linked to the adaptability of large-scale network structure.

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**Poster**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** Italian Ministry of Health, grant number Rf-2011-02349953

**Title:** Age-related differences in brain activation during the acquisition and retention of a visuomotor skill

**Authors: *K. M. BERGHUIS**[1,4], S. FAGIOLI[4], N. M. MAURITS[2], I. ZIJDEWIND[3], T. HORTOBÁGYI[1], G. KOCH[4], M. BOZZALI[4]
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**Abstract:** Learning new motor skills and re-learning motor skills during rehabilitation from an injury are abilities needed throughout the lifespan. In this study, we examined the age-related changes in brain activation during visuomotor skill acquisition and retention. Healthy young (n = 17, 10F, age mean 25.5 years) and older adults (n = 16, 7F, mean age 62.6 years) performed a visuomotor tracking task, using flexion and extension of the right-dominant wrist, while lying in an MRI scanner. On Day 1, participants performed a pre-test, a training session and a post-test. On Day 2 (24h later) participants performed a retention test. Testing consisted of 6 blocks of 5 trials of both the experimental (zig-zagged template) and control task (monotonically increasing or decreasing line) with each trial being 4, 5 or 6 s. The training session consisted of 120 trials of

the experimental task, inside the MRI scanner. FMRI acquisition only took place during the test sessions (Siemens Allegra, 3T, 279 volumes per test). Old (error: 14.5°) compared with young adults (error: 9.7°) performed more poorly at the pre-test on the visuomotor tracking task but practice improved both age-groups' performance to a similar extent (young: 26%, old: 31%). Performance of both age groups remained stable at retention. Preliminary fMRI data analysis in 15 young and 12 old adults showed a main effect of Time on activation in the right middle occipital gyrus, while there was no main effect of Age on brain activation. There was an Age*Time interaction in bilateral precuneus activation, with increases in activation in this area from pre- to post-test in young but not in old adults. However, in old adults, activation decreased from pre- to post-test in a more superiorly located part of the precuneus. At retention, the activation in the precuneus returned to pre-test levels in both age groups. These results suggest that the precuneus is differently activated in young and old adults during the acquisition and retention of a visuomotor skill.

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**Poster**

**525. Human Motor and Sequence Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 525.05/VV1

**Topic:** H.02. Human Cognition and Behavior

**Support:** NHMRC Project Grant APP1078464

**Title:** tACS-applied slow-wave oscillations enhance repeated plasticity paradigm effects

**Authors: *C. BRADLEY**[1], G. KIESEKER[1], J. B. MATTINGLEY[1,2], G. TONONI[4], M. V. SALE[3]
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**Abstract:** If two plasticity paradigms are applied in close succession, response to the second paradigm is reduced compared with when it is administered on its own. This effect is thought to arise from saturation of synaptic connections by the preceding plasticity event. Slow-wave sleep has been hypothesized to "unload" synapses, allowing greater plasticity to occur with subsequent plasticity paradigms. Here we examined whether this unloading effect could be mimicked using non-invasive electrical brain stimulation. Specifically, we ask whether artificial induction of slow waves in awake humans allows successive plasticity protocols to exert their full effects. Thirty healthy adult participants underwent two successive plasticity protocols: (1) a motor training task (30 min ballistic thumb abduction, 0.5Hz), and (2) a paired associative stimulation

(PAS), “excitatory” paradigm involving near-synchronous stimulation of the median nerve and primary motor cortex (M1; 133 stimuli at 0.2Hz). Plasticity within the corticospinal motor tract was quantified indirectly by measuring motor evoked potential (MEP) amplitude elicited by single pulses of transcranial magnetic stimulation (TMS) over left M1. In between the two plasticity paradigms, participants received transcranial alternating current stimulation (tACS, 1mA, 3 x 6-minute exposures, 1 min break intervals) targeting left M1. Crucially, tACS was delivered at a slow wave frequency (0.75Hz), under active or sham (no stimulation) conditions. Each participant underwent two separate sessions, in a double-blind, randomised cross-over design. As expected, motor training significantly increased MEPs in the target muscle (~165% of baseline amplitude, $p<0.01$) by a similar amount for both the active and sham tACS sessions. Importantly, MEP amplitude was modulated differently following sham versus active tACS (ANOVA interaction, $p=0.01$). Specifically, MEPs were significantly larger after sham than after active tACS ($p=0.04$). Consistent with existing literature, the PAS plasticity protocol following motor training did not result in further modulation of MEPs in the sham session, suggesting a saturation of targeted synapses. In contrast, when active tACS was applied after motor training, PAS had a significant facilitatory effect on MEPs ($p=0.02$). These results provide evidence for modulation of motor cortex plasticity by low-frequency, slow-wave-like non-invasive electrical stimulation in the awake human. We speculate that slow-wave tACS plays a similar role to slow-wave sleep by re-setting synaptic connections that have been potentiated, permitting them to respond to successive plasticity paradigms.

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**Poster**

**525. Human Motor and Sequence Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 525.06/VV2

**Topic:** H.02. Human Cognition and Behavior

**Title:** Individual differences in implicit probabilistic sequence learning

**Authors: *S. A. KISER**[1], P. KHOSRAVI[2], N. E. ADLEMAN[2]
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**Abstract:** Emotion regulation, mood, and attention have been shown to influence learning and memory. However, their effect on implicit probabilistic sequence learning (IPSL) has yet to be determined. IPSL is fundamental to adaptive behavior and results from knowledge gained from the probabilistic structure of events. Many skills, such as written and spoken language, driving, cooking, and performing sports or music comprise such ordered regularities. Therefore, it is

important to understand the interaction between IPSL and other cognitive processes. The current study aimed to investigate the role emotion regulation, mood, and attention play in probabilistic sequence learning in a Triplets Learning Task (TLT). Specifically, we investigate: 1.) the relationship between IPSL and self-reported emotion regulation, mood, and attention, and 2.) whether attention control mediates these relationships.
Twenty-one healthy college-aged (20.76±1.34) students (12 female) completed questionnaires related to Mood Regulation (MR), Depression & Anxiety (DA) symptoms, Attention & Impulsivity (AI), and were administered a TLT via a touch-screen tablet.
Results from the TLT revealed that subjects learned to predict high probability events. Overall response times improved with practice ($F(1.67,31.67)=16.54$, $p<0.001$), were fastest for high probability events ($F(1,19)=24.54$ $p<0.001$), and a trend interaction between event frequency and practice ($F(5,95)=2.13$, $p=0.069$) showed responses to high probability events improved most with practice. A recognition test showed no subjects were aware of event frequencies.
Correlation analyses returned no significant relations between TLT learning scores (LS) and self-reported medical, neurological, or attention deficit diagnoses. However, regression analyses revealed a significant relationship between Depression & Anxiety measures and LS ($F(2,17)=3.88$, $R^2=0.313$, $p=0.041$). Measures of MR and AI failed to predict LS.
Mediation analyses were performed to determine if Attention Control (AC) using the Attention Control Scale mediated the relationship between Depression & Anxiety and Learning Scores. Results revealed a trend where DA predicted AC ($F(2, 17)=2.99$, $R^2=0.26$, $p=0.077$); however, AC was not a mediator of DA and LS. Three explanations could account for these findings: 1) N not sufficient to power the analysis, 2) range of scores were too limited, 3) DA could affect both AC and LS.
In conclusion, DA appears to predict IPSL performance, yet our results do not implicate attention as mediator. Future studies should be aware that mood could influence IPSL, which could affect learning new skills and engaging in adaptive behaviors.

**Disclosures: S.A. Kiser:** None. **P. Khosravi:** None. **N.E. Adleman:** None.

**Poster**

**525. Human Motor and Sequence Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 525.07/VV3

**Topic:** H.02. Human Cognition and Behavior

**Title:** Gaze-hand coordination and learning in an unpredictable competitive marksmanship task

**Authors: *N. J. STEINBERG**[1], L. F. SCHETTINO[2], A. A. BROWN[3]
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**Abstract: Purpose:** Marksmanship and competitive shooting tasks require active engagement and demand high levels of hand-eye coordination. Training can improve performance, but how? Gaze control learning has improved performance in sporting events that employ Quiet Eye, a form of gaze fixation where the object is fixed, such as in basketball (Harle & Vickers, 2001), darts (Vickers, Rodrigues & Edworthy, 2000), and shotgun shooting (Causer et al., 2010). Gaze control training has not yet been shown for Smooth Pursuit Eye Movements (SPEM), or for unpredictable ballistic target motion. Furthermore, the purpose of the present study was to provide insight into which strategy participants used to track targets: chasing, one in which humans follow the trajectory of the target (Hoffman, 1991), or ambushing, when humans anticipate where the target will be in the future and wait there (Tresilian, 2005).
**Method:** This study used a simulated 3-Gun competitive shooting event (Brown, 2016) involving what is colloquially known as the *Death Star*. The Death Star requires individuals to hit five steel plates that rotate and swing on a double-hinged target. The simulation used non linear equations that mimic the actual event and it was sensitive to internal conditions; the timing and location in which a plate is hit influences its path. As such, no two trials are alike. The star's swift and unpredictable movements makes this event engaging and it requires one's full attention to learn the task. Twenty two naïve participants attempted 20 trials over 6 training days. Half of them received gaze control training while the others did not. Participants stood three meters away and shot the targets with a plastic pistol outfitted with a laser pointer and wore a head mounted eye tracking system. Participants also played a round of Darts before and after the study to investigate if ability was transferred between tasks.
**Results:** The present study found evidence for both chasing and ambushing strategies. Both strategies efficiently tackled the complexity of the Death Star task under our experimental conditions. The present study is also the first demonstrate that two-dimensional, unpredictable target tracking can be improved through gaze control training. Additionally, we found that this skill was transferable between a dynamic and stationary target tracking task.

**Disclosures: N.J. Steinberg:** None. **L.F. Schettino:** None. **A.A. Brown:** None.

**Poster**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH T32 Training Grant #5T32HD055180-08

**Title:** Discovery-based learning affords neural facilitation enhancing generalization to a novel motor task

**Authors: *R. LAWSON**[1], J. JOHNSON[2], L. WHEATON[2]
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**Abstract:** Prior studies have shown that the presence of explicit awareness in motor learning is detrimental to generalization, a key aspect for flexibility in motor skill acquisition. However, as most of these studies have utilized an intentional paradigm to elicit awareness, it is unclear if awareness developed incidentally results in the same detrimental effects on generalization. A recent study by our lab demonstrated the presence of a facilitative network for subjects demonstrating explicit awareness during a motor learning task. This network may provide individuals with improved neural connections which enhance the ability to quickly identify efficient motor heuristics in a novel environment. The purpose of our study was to examine the effect of priming subjects to a level of incidental explicit awareness on the ability to transfer to a novel, more complex motor task. To this end, subjects assigned to a priming condition experienced a 7-element serial reaction time task and then transferred to a 10-element sequence. Subjects in the control condition (CONTROL) experienced just the 10-element sequence without priming. Utilizing our behavioral indicator for the presence of incidentally developed explicit awareness, primed subjects were classified as explicit (EXP) or non-explicit (NOEXP) to the order of the 7-element sequence. Results show that over 50% of the EXP subjects developed explicit awareness of the 10-element sequence, as compared to less than 10% of the NOEXP or CONTROL subjects. EEG data analysis demonstrates a neural shift for both the EXP and NOEXP subjects in the 10-element sequence as compared to the CONTROL group, demonstrating neural changes associated with the priming effect of the initial 7-element sequence. Primed subjects failing to develop awareness on the 10-element sequence significantly differed from the EXP and CONTROL group in neural patterns suggesting that successful transfer may require a balance of sensory and motor processing afforded by the facilitative network utilized in the initial discovery learning. The current results reveal the beneficial effects of explicit awareness developed in a discovery-based paradigm on generalization.

**Disclosures: R. Lawson:** None. **J. Johnson:** None. **L. Wheaton:** None.

**Poster**

**525. Human Motor and Sequence Learning**

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**Program#/Poster#:** 525.09/VV5

**Topic:** H.02. Human Cognition and Behavior

**Support:** NSERC Grant RGPIN-2014-04465

**Title:** Implicit & explicit knowledge in visual statistical learning

**Authors: *K. HIMBERGER**[1], A. S. FINN[2], C. J. HONEY[1]
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**Abstract:** *Background*: Statistical learning, the process of extracting regularities from the environment, is believed to produce both "implicit" and "explicit" knowledge (Batterink et al, 2015; Turk-Browne et al, 2005). Implicit knowledge is revealed indirectly, as in facilitation of the reaction time (RT) for predictable elements in a target detection stream (Schacter, 1992). Explicit knowledge is directly measured, and may also be the dominant influence in the two-alternative forced choice (2AFC) recognition procedure that is widely used to assess statistical learning (Batterink et al, 2015). In light of proposed connections between statistical learning and implicit learning (Perruchet & Pacton, 2006), it is important to understand which kinds of knowledge contribute to which tests. Therefore, we asked: (i) is 2AFC recognition performance driven by explicit knowledge even for visual sequence learning that occurs incidentally during a cover task?; and (ii) how are the contributions of implicit and explicit knowledge altered when the timing of stimulus presentation changes?
*Methods*: We conducted a series of online experiments in which participants viewed visual streams composed of four sets of image triplets (5-12 minutes of exposure), while performing a "jiggle detection" task (Turk-Browne et al, 2009). Participants then completed three tests: (1) target detection; (2) 2AFC familiarity; (3), explicit triplet creation. Stimuli were presented either speeded (200ms duration; 40ms ISI) or unspeeded (800ms duration; 200ms ISI).
*Results*: Mean 2AFC performance varied between 54 and 56% across conditions. There was substantial individual variability in both RT facilitation and 2AFC performance within each condition. Across all conditions, 2AFC performance was correlated with the ability to subsequently "create" parts of triplets or entire triplets. Conversely, the more implicit measure of learning (RT facilitation) was not correlated with the ability to create triplets. Preliminarily, speeded stimulus presentation and testing appeared to decrease 2AFC performance and increase RT facilitation.
*Conclusions*: Our results are broadly consistent with those of Batterink et al. (2015), who argued for dissociable contributions of explicit and implicit knowledge on 2AFC performance and RT facilitation. We extend these findings to visual stimuli presented under a cover task, and find tentative evidence that speeding the stimuli during test leads to a greater contribution of implicit knowledge. Future work will explore stimulus timing (independently varying stimulus duration and ISI) and the possible effects of acquiring explicit knowledge during testing.

**Disclosures: K. Himberger:** None. **A.S. Finn:** None. **C.J. Honey:** None.

**Poster**

**525. Human Motor and Sequence Learning**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NHMRC Project Grant APP1078464

**Title:** tACS-applied slow wave oscillations promote consolidation of motor cortical plasticity in the awake human brain

**Authors: *M. V. SALE**[1], N. BLAND[2], C. BRADLEY[3], G. TONONI[4], J. B. MATTINGLEY[3]
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**Abstract:** Slow wave sleep is thought to play an important role in consolidating plastic changes (e.g., memories, learnt skills) that arose during the preceding period of wakefulness. These processes for consolidating plastic change are believed to manifest from the high amplitude, low frequency oscillations in cortical excitability that are present during slow wave sleep. Non-invasive brain stimulation (transcranial alternating current stimulation; tACS) has been shown to mimic these slow oscillations, and can affect learning in the *awake* state. This suggests that induced slow oscillations can affect plasticity without the need to sleep. Here, participants (n = 20) received slow (0.75Hz) oscillatory active tACS to left motor cortex for 15 minutes, or sham stimulation, in separate sessions. Prior to tACS, participants received a repetitive transcranial magnetic stimulation (rTMS) paradigm to induce a long-term potentiation-like change in synaptic efficacy to motor cortex. Plasticity was quantified indirectly by measuring the amplitude of motor evoked potentials (MEPs) from single-pulse TMS at several time-points: before rTMS, after rTMS (before tACS), and then every 5 minutes for 30 minutes after tACS. As expected, MEP amplitude increased significantly and to an equivalent level following rTMS in both active and sham conditions. Following sham tACS, however, MEP amplitude returned to baseline levels. Critically, MEPs following active tACS remained elevated at least 30 minutes after stimulation ceased. This suggests that slow oscillatory tACS can consolidate the plasticity induced in human motor cortex, and mimics the effects of slow wave sleep, without the need for sleep. These findings have important implications for our understanding of the physiological basis of slow wave sleep, and could have translational value for neurological rehabilitation. For example, it may be possible to promote consolidation of learnt skills etc. by applying slow oscillatory tACS to improve motor recovery after stroke, or in patients with cognitive deficits.

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**Poster**

**525. Human Motor and Sequence Learning**

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**Program#/Poster#:** 525.11/VV7

**Topic:** H.02. Human Cognition and Behavior

**Support:** FRQ-S

NSERC

**Title:** Static magnetic field stimulation alters motor learning in humans

**Authors: *A. LACROIX**[1], L. PROULX-BÉGIN[2], F. MORIN-PARENT[1], J.-F. LEPAGE[1]
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**Abstract:** An increasing number of studies show that static magnetic fields (SMF) can modify brain activity by reducing neuronal excitability. Evidence for this comes mainly from neuroimaging studies, but data showing the ability of SMF to alter human behaviour is scarce. Here, we used the serial reaction time task (SRTT), a task known to be sensitive to common non-invasive neuromodulatory tools, to assess the efficacy of SMF to modulate sequence motor learning. Twenty right-handed adults performed the SRTT while a 50mm neodymium magnet (N42) or a placebo was applied to the primary motor cortex of the left hemisphere. Results show a marked decrease in learning rate for participants in the real-magnet condition, affecting reaction time in sequence blocks ($p<0.001$) without altering reaction time for random blocks ($p > 0.1$). These results show that SMF applied to the motor cortex can potently alter the neurophysiological processes involved in motor learning, validating the utility of SMF stimulation for cognitive studies in humans.

**Disclosures: A. Lacroix:** None. **L. Proulx-Bégin:** None. **F. Morin-Parent:** None. **J. Lepage:** None.

**Poster**

**525. Human Motor and Sequence Learning**

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János Bolyai Research Fellowship of the Hungarian Academy of Sciences (KJ)

**Title:** Intrinsic EEG functional connectivity in theta band is associated with individual differences in statistical learning

**Authors: *Z. KARDOS**[1], B. TOTH[2,5], A. KÓBOR[3], A. TAKACS[6,7], K. JANACSEK[7,4], D. NEMETH[7,4]
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**Abstract:** Statistical learning is crucial for obtaining motor, cognitive, and social skills. Accumulating evidence suggests that the spontaneous intrinsic (resting state) functional connectivity (FC) between regions of the brain may contribute to the capacity of the nervous system for acquiring probabilistic knowledge. The present study aimed to investigate resting-state FC and its relationship with statistical learning performance on a widely used probabilistic learning task (the Alternating Serial Reaction Time, ASRT) task. It was hypothesized that intrinsic FC of the frontal and temporal brain regions exclusively in the theta rhythm (4-7 Hz) promote the individual's learning capabilities. 64-channel EEG was recorded for 5 minutes during a resting period (eyes-opened) before the participants performed the ASRT task. FC between 62 source reconstructed cortical regions was measured by phase synchronization index (PLI) within theta band. Significant positive linear correlation was evident between the FC of the medial frontal gyrus and a statistical learning index, suggesting that increased frontal connectivity in theta band during the pre-learning period predicts better performance in statistical learning. The present results further emphasize the role of trait characteristics function of the fronto-parietal network in the extracting regularities from the environment.

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**Poster**

**525. Human Motor and Sequence Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 525.13/VV9

**Topic:** H.02. Human Cognition and Behavior

**Support:** Doctoral Scholarship, Conicyt, Chile

**Title:** Frequency-dependent modulation of motor adaptation by cerebellar transcranial alternating current stimulation

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**Abstract:** Motor adaptation involves contributions from multiple cortical and subcortical regions of the human brain, organized in widespread networks. In this learning process, cerebellum seems to play a major coordinating role, synchronizing large-scale interregional systems. We report a study where 18 participants carried out a visuo-motor task under the impact of cerebellar Transcranial Alternating Current Stimulation (tACS) using 20 Hz, 50 Hz or sham tACS delivered at 2mA for ~12 minutes. Participants must perform a reaching task with the right arm to bring a central dot towards a target distributed across eight eccentric locations. In parallel, participant's motor responses had to compensate a 45° counter-clockwise distortion of the screen's visual feedback on online target location, while being under the effects of one of the tACS conditions. Kinematic analysis of individual trials allowed the identification of two sub-groups of ballistic arm responses: *accurate responses* (i.e., movements that reached the target in time) and *erratic responses* (i.e., responses in which the target was undershot or overshot at the end of response window). Analysis of *erratic responses* across tACS conditions revealed for the 50 Hz tACS a significant decrease of the kinematic error, and a faster adaptation process to visual distortions across trials. Such effect proved specific for reaching movements towards targets displayed in the upper left and upper right side of the screen (but not for those displayed in the lower left and right-sided locations). No significant effect of tACS condition was found for any of the tested metrics indexing motor adaptation for *accurate responses*. Our results provide support to the notion of a direct modulatory enhance of error processing conducted by the cerebellum, likely induced by a local entrainment of frequency specific rhythmic activity at 50 Hz. Moreover, our data support future promise for cerebellar tACS for the modulation of motor adaptation in healthy participants and also neurological patients with impaired motor learning abilities.

**Disclosures: J.J. Mariman:** None. **D. Rojas-Líbano:** None. **A. Valero-Cabré:** None. **P.E. Maldonado:** None.

**Poster**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH grant R15MH106957

**Title:** Investigating the role of the cerebellum in motor, linguistic, and social prediction: A tDCS-fMRI study

**Authors: *C. J. STOODLEY**[1], S. E. MARTIN[2], B. C. DRURY[2], A. M. D'MELLO[1]
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**Abstract:** Clinical, neuroanatomical, and neuroimaging data suggest that the human cerebellum is involved in cognitive and social processing as well as motor control. However, the precise contribution of the cerebellum to cognitive and social processes has yet to be established. Based on the motor literature, we hypothesize that the cerebellum builds internal models that are used to optimize performance and predict upcoming stimuli, leading to improved accuracy and faster response times. Here, we combine transcranial direct current stimulation (tDCS) and functional neuroimaging (fMRI) to investigate the role of the right posterolateral cerebellum in predictive processing in motor, linguistic, and social domains. Healthy young adults (all male; mean age 21.6±2.3 years) completed three tDCS-fMRI sessions. In each session, participants received 20min of 1.5mA anodal, cathodal, or sham tDCS over the right posterolateral cerebellum (1cm down and 4cm to the right of the inion). Then, participants completed three task paradigms, each with both non-predictive and predictive components: a serial response time task (SRTT), a sentence completion task, and a social ball-playing task. Task and modulation conditions were counterbalanced within and between participants, and repeated-measures analyses were conducted. We hypothesized that cerebellar tDCS would specifically impact performance on trials requiring implicit predictive processing (i.e. sequence learning blocks during the SRTT, highly predictive sentences during the sentence completion task, and learning which player had the highest probability of being a good partner on the social ball-playing task). Results suggest that cerebellar tDCS affected performance on trials in which prediction was necessary (e.g. sequence but not random trials on SRTT). Initial imaging results indicate that cerebellar tDCS had anticipated effects on BOLD signal based on tDCS polarity, with anodal tDCS and sham conditions showing increased right posterolateral cerebellar activation relative to cathodal tDCS (e.g. language task; $p<0.001$, FDR 0.05). There was also increased basal ganglia and primary motor cortex engagement during the SRTT when cerebellar activation was modulated ($p<0.001$, FDR 0.05), indicating a potential compensatory effect to maintain task performance. These findings support the hypothesis that the cerebellum is involved in implicit predictive processing across a range of tasks.

**Disclosures: C.J. Stoodley:** None. **S.E. Martin:** None. **B.C. Drury:** None. **A.M. D'Mello:** None.

**Poster**

**525. Human Motor and Sequence Learning**

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**Topic:** H.02. Human Cognition and Behavior

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Stiftung zur Förderung der gastroenterologischen und allgemeinen klinischen Forschung sowie der medizinischen Bildauswertung Grant 2015/01

**Title:** Functional connectome changes induced by working memory and motor sequence trainings

**Authors: *S. MAGON**[1,2], P. ZUBER[2], L. GAETANO[1,2], A. GRIFFA[3], M. HUERBIN[2], L. PEDULLÀ[4], L. BONZANO[5], P. HAGMANN[3], J. WUERFEL[2], T. SPRENGER[6], O. SPORNS[7], L. KAPPOS[1]
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**Abstract: Background.** There is evidence that motor sequence learning (MSL) is related to working memory (WM) abilities. However, a potential interaction between WM and MSL trainings has not been investigated so far. **Aim.** We aimed at evaluating the differences in brain functional connectivity (FC) induced by two sequential training programs (WM + MSL and MSL + WM) and a combined program (WM and MSL in the same session). In the first setting the purpose was to quantify the additive effects. In the second case we analysed the interaction effects. **Methods.** Fifty-four healthy subjects (27 women; mean age: 30.2±8.6) were pseudo-randomly assigned to the three training programs. In total all subjects had four MRIs. Two MRIs were done prior to the trainings, a third MRI after three weeks and a fourth after six weeks of training. Each participant conducted all 24 training sessions at home using touch-screen devices. The MRI protocol included a 3D T1-weighted (MPRAGE, voxel size=0.7x07x07mm), and a multi-band EPI sequence (voxel size=2x2x2mm, TR=768 ms with 1160 repetitions) acquired on a 3T scanner. The FC matrices were generated by parcellating the brain in 234 regions and computing the cross-correlations among the resting-state fMRI signal in all regions. Differences in the strength of FC between sessions were computed in the whole sample by using the network-based statistic (NBS) algorithm. Differences among subgroups were investigated by computing the effect size (Cohen's *d*) between each pair of nodes of the network identified in the whole sample analysis. **Results**. The comparisons performed on the whole sample between the first and fourth MRI showed increased FC after the training in the parieto-fronto-temporal network. Within this network, the right inferior parietal gyrus showed increased FC with the right middle temporal gyrus, the right orbitofrontal gyrus and the right hippocampus. The left posterior-superior temporal and the precentral gyri showed increased FC with the right superior parietal and the supramarginal gyri and the right insula. No differences were observed between the two pre-training MRIs. The analysis of the effect size showed higher FC changes between

left temporal and right parietal regions for the combined program, between left temporal and bilateral parietal regions for the WM + MSL program and between right fronto-parietal regions for MSL + WM program. **Conclusion**. Sequential and combined training programs produced distinct patterns of FC modulation suggesting a relevance of the order in which trainings are performed. These observations provide new insight to plan effective training/rehabilitation programs.

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**Poster**

**525. Human Motor and Sequence Learning**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** KTIA NAP 13-2-2015-0002 (DN)

Postdoctoral Fellowship of the Hungarian Academy of Sciences (AK)

János Bolyai Research Fellowship of the Hungarian Academy of Sciences (KJ)

**Title:** ERPs differentiate the sensitivity to raw statistical probabilities and the learning of sequential structures during probabilistic sequence learning

**Authors: *A. KÓBOR**[1], Á. TAKÁCS[2,3], Z. KARDOS[4,6], K. JANACSEK[3,5], K. HORVÁTH[3], D. NEMETH[3,5]
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**Abstract:** Probabilistic sequence learning enables the sensitivity to and the extraction of statistical regularities embedded in the environment; therefore, it plays a crucial role in the acquisition of automatic behaviors, such as skills and habits. Although several processes contribute to the overall learning performance that can be measured with overt behavioral responses in skill learning tasks, the temporal dynamics of neural mechanisms underlying these different learning processes have remained unclear. Therefore, we investigated whether two prominent learning processes - statistical learning and the learning of sequential structures - can

be distinguished using event-related brain potentials (ERPs) during probabilistic sequence learning. Healthy young adults (N = 40) performed the Alternating Serial Reaction Time (ASRT) task while EEG was recorded with 64 electrodes. The ASRT task is a unique tool to investigate the learning of raw statistical probabilities as well as more complex sequential structures within the same experimental design. We measured RTs and ERPs time-locked to the onset of the stimulus. At the behavioral level, while raw statistical probabilities were acquired rapidly, the learning of sequential structures developed gradually during the task. ERPs also reflected the distinct trajectory of these two mechanisms. Although the N2 component showed rapid, automatic detection of raw statistical probabilities, it gradually changed as participants acquired the sequential structures. ERP modulation related to the processing of raw statistical probabilities and sequential structures was also observed at the early stage of perceptual processing as the P1 component was sensitive to both mechanisms and this sensitivity did not change with practice. Overall, the N2 was elicited when the actual stimulus deviated from the predicted one that followed from the previously established representation of statistical contingencies experienced in the given environment. In addition, exposure to probabilistic regularities altered selective attention and thereby early visual processing of stimuli. In sum, our results indicate that statistical learning and the learning of sequential structures develop differently at the neural level. These findings could be interpreted in the broader framework of predictive theories and might provide insight to the dynamic change of multiple processes that occur during sequential memory formation.

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**Topic:** H.02. Human Cognition and Behavior

**Support:** Clinical Hospital FMUSP

**Title:** Transcranial direct current stimulation improves the learning, retention and generalization of a new motor skill involving finger opposition sequence movements in healthy adults

**Authors: *M. E. PIEMONTE**[1], A. ZOMIGNANI[2,3], J. MOREIRA SANTOS[4], T. SILVA MARTINS[4], R. SILVA MARTINS[4], M. F. MENEGATTI[4]
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**Abstract: Aim:** To verify the effects of transcranial direct current stimulation (TDCS) on the learning, retention and generalization of a new motor skill involving finger opposition sequence movements in healthy adults **Methods:** The present study compared the motor performance in terms of speed and accuracy, on two sequences of 5 opposing finger movements, where one sequence was trained (TS) and the other was not (NTS). Comparisons were made before (BT), 5 minutes (AT), 48 hours (48AT) and 7 (7DT) and 28 (28DT) days after a single training session, split into 4 blocks of 600 movements, in 20 healthy subjects with mean age of 20.8 years (SD=2.1), randomly allocated in an experimental group, which received 20 minutes of TDCS (2ma), concomitantly the training, and a control group, which received a placebo TDCS, concomitantly the training too. After the end of training, the performance was assessed under exactly the same conditions used in the previous assessments. The results were analyzed by RM ANOVA using as factors 2 groups (EG;CG) X 2 sequences (TS;NTS) X 5 assessment points (BT; AT; 48AT; 7AT; 28AT), which the two last were considered as repetitive measure **Results:** The analysis of performance, in terms of number of correct sequences showed a significant interaction amongst group, assessment and sequence ($F(15,18) = 2.58$, $p < .001$, ES=.90). **Conclusion:** The TDCS applied concomitantly the motor training improve the motor learning even in healthy adults, suggest that the increased cortical excitability mediate by TDCS can facilitate the mechanisms of synaptic reorganization associated to the learning process

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**Poster**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** ACSM Foundation Doctoral Student Research Grant

**Title:** Impact of error magnitude on sensorimotor skill performance changes before and after consolidation

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**Abstract:** The period following sensorimotor skill acquisition, known as consolidation, is a necessary aspect of skill learning in health and disease. However, multiple practice sessions are often required for sensorimotor skill mastery and error reduction. While the adaptation to errors in skill performance is important to improve performance and learning, little is known about how error impacts performance before versus after the occurrence of consolidation. The objective of

this study was to determine differences in the impact of error during sensorimotor skill performance before and after a period of consolidation. Fifteen healthy right handed young adults (18-35 yrs) participated. The training protocol involves repetitive throwing of a small ball using the non-dominant upper extremity to five unique visuospatial targets while seated. Testing blocks consist of a random presentation order of the targets (e.g. target 1, 5, 3, 2, 4), whereas training blocks consist of blocked presentation order of the targets (e.g. target 2, 2, 2, 2, 2). Spatial metrics of throwing accuracy during testing blocks were collected at four time points (baseline, post initial training session, post one hour interval, and post second training session). Results show that, after normalizing training block throwing error distance and testing block change scores to baseline performance, the magnitude of error during training was significantly negatively correlated with within-initial training session performance change score ($r = 0.704$, $p = 0.005$). However, following the 1 hr consolidation period, the magnitude of error during training was less negatively correlated with within-second training session performance change score ratios ($r = 0.459$, $p = 0.085$). These findings suggest that error during sensorimotor performance may become more useful for fine-tuning skill performance over time following consolidation. A larger study with increased subjects is now underway. Future research will investigate the impact of various activities performed during the consolidation phase on the subsequent importance of error to sensorimotor skill performance.

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**Poster**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** BMBF Grant 01EO0901 (DSGZ)

**Title:** Intersubject-similarity of BOLD activity while learning to fold origami

**Authors: *K. KOSTORZ**[1,2], V. L. FLANAGIN[1,2], S. GLASAUER[3,1,2]
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**Abstract:** In today's web-based society, information on 'how something is done' can be found easily and quickly: Platforms like YouTube offer the possibility for everyone to upload self-made instructive videos which anybody interested can watch and thus learn by observing and imitating the seen content. Here we investigated this media-based approach of human observational learning using fMRI: a highly trained instructor folded an origami inside the MRI

scanner while being videotaped. We took care that the content of the video was instructive by making sure all steps were well visible and the folding was performed at a moderate pace. In the scanner, the instructor performed the origami without vision while being blindfolded. As a control, the instructor folded similar but partly repetitive folds while being videotaped and scanned.
For the preliminary results reported here, 19 subjects viewed the instructive video three times inside the MRI with the task to memorize the steps leading to the final origami. Right after each video, they had to reproduce the origami as far as they could. While watching the control video of the repetitive folds, subjects had to count the number of folds being made to ensure cognitive load and attentiveness. We assessed similarity using the intersubject-correlation method (Hasson et al. 2004) and the intersubject-correlation toolbox (Kauppi et al. 2014).
We found similar activity between the blindfolded instructor and the mean action observer in the action observation network in all conditions. This highlights similar activity when performing a complex naturalistic task and when observing it, even though similarity due to visual feedback can be ruled out, since it was not available for the instructor. (Out of the 19 subjects, only one detected the blindfold, which ensures that the naturalistic context was kept.)
The action observation network was also involved in all viewings when comparing between-observer similarity. However, average between-subjects correlations were significantly higher in the action observation network for the 'learning' conditions than the 'count folds' condition. This was the case also for the third repetition of watching the video, even though reported attentiveness was on average smaller than in the 'count folds' condition. This demonstrates a new facet of action observation network engagement: similarity of activity while learning a bimanual naturalistic task, with higher similarity of activity than during a task of visual-spatial processing and action identification.

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**Poster**

**526. Aging and Memory**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant R01AG048076

**Title:** Cortical and hippocampal predictors of individual differences in episodic memory in putatively healthy older adults

**Authors:** ***A. N. TRELLE**[1], J. BERNSTEIN[3], V. A. CARR[4], C. FREDERICKS[1], S. GUERIN[1], W. GUO[1], M. JAYAKUMAR[1], J. JIANG[1], G. KERCHNER[2], A. KHAZENZON[1], C. LITOVSKY[5], S. SHA[2], M. THIEU[1], A. WAGNER[1]

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**Abstract:** Older adults frequently experience declines in memory for personally experienced events, or episodic memory. However, the degree of memory decline varies considerably across individuals, even among putatively healthy older adults who do not meet clinical criteria for cognitive impairment. The present study seeks to investigate how hippocampal and cortical mechanisms supporting episodic memory relate to variation in memory performance among healthy older adults (60-90 yrs). This multi-modal study included the following measures: neuropsychological testing, high-resolution whole-brain 3T functional MRI with hippocampal subfield segmentation, hippocampal microstructure defined by ultra-high resolution 7T MRI, as well as genetic (APOE ε4) and molecular (CSF tau, beta-amyloid) biomarkers of Alzheimer's disease (AD). In the high-resolution fMRI study, participants were scanned during encoding and retrieval phases of an associative memory task. During encoding, participants were presented with a series of word-picture associations. During retrieval, participants were presented with studied words intermixed with new words, and asked to recall the specific picture paired with each word. The memory test included measures of both associative (source) and item memory: participants indicated the category of the paired associate (face or scene) if they could recall it successfully or, if they failed to remember the associate, had the option to classify the word as "old" (item memory only), or "new". Preliminary analyses (N = 31) targeted cortical reinstatement in ventral occipitotemporal cortex (VOTC; parahippocampal, fusiform, and inferior temporal cortex) during correct source memory retrieval. A logistic regression classifier was trained to discriminate between face and scene multi-voxel patterns in VOTC during encoding. The trained classifier was then tested on recall data; classifier performance at recall was treated as a measure of cortical reinstatement. Individual differences in source memory accuracy were partially accounted for by differences in cortical reinstatement (R-squared = .34; $t(29) = 3.82$; $p = .001$), even after controlling for the effects of age (R-squared-change = 0.31; $t(28) = 3.61$, $p = .001$). These preliminary findings suggest that individual differences in associative memory performance are linked to differences in cortical reinstatement during memory retrieval. Ongoing analyses will integrate multi-modal measures of medial temporal lobe structure, function, and AD biomarkers to explain the mechanisms underlying individual differences in episodic memory performance in older adults.

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**Poster**

**526. Aging and Memory**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** DANA Foundation

James S. McDonnell Foundation

**Title:** Playing 3D video games can improve memory and hippocampal structure in older adults

**Authors: *G. D. CLEMENSON**, C. E. STARK
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**Abstract:** It is well understood that simply exposing rodents to a larger and more stimulating environment can have a positive impact on hippocampal neuroplasticity and function. This manipulation, known as environmental enrichment, has been shown to ameliorate and even rescue deficits in the hippocampus associated with aging. We are interested in whether this environmental enrichment manipulation has relevance to humans and can improve the structure and function of the hippocampus within an aging population of humans. Previously, we showed that playing 3D video games (Super Mario 3D World) can enhance hippocampus-associated behaviors in young adults and may act as a human correlate of environmental enrichment. Here, we further investigate the potential of video games as an intervention to mitigate cognitive and structural decline associated with aging in the hippocampus of older adults. We train an older population of naïve gamers in the video game Super Mario 3D World for one month. Participants are subject to pre- and post- testing sessions including a neuropsychological battery, high resolution structural and diffusion imaging brain scans, and a hippocampal-dependent mnemonic discrimination task. Preliminary results show that participants who played Super Mario 3D world demonstrated an enhancement in their mnemonic discrimination ability and this improvement was positively correlated with volumetric changes in hippocampal gray matter from pre-test to post-test with the dentate gyrus showing the most reliable changes. These data suggest that playing specific types of modern video games may have a meaningful impact on hippocampal deficits associated with aging.

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**Poster**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant 1R01AG039103

**Title:** The relationships between global cortical thickness, intra-scan motion and recognition memory performance as a function of age

**Authors: *M. A. DE CHASTELAINE**[1], D. D. R. KING[2], B. E. DONLEY[2], K. M. KENNEDY[2], M. D. RUGG[3]
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**Abstract:** The relationship between global cortical thickness and cognitive performance is moderated, non-monotonically, by age. Moreover, it has recently been reported that head motion during MR scanning can systematically underestimate measures of cortical thickness. Here, we investigated the effects of head motion on estimates of global cortical thickness and the relationship between cortical thickness and memory performance (controlling for motion) on associative recognition performance in three age groups encompassing much of the adult lifespan (young, middle-aged and older adults; total n = 133). Measures of global cortical thickness were obtained using a semi-automated method, and an index of mean head motion obtained during functional scanning was employed as a proxy for head motion during the structural scan. In addition to decreased memory performance, older age was associated with increased motion and cortical thinning (both before and after controlling for head motion). Amount of head motion was negatively associated with memory performance in young and middle-aged, but not older, participants, while cortical thickness was negatively associated with memory performance in the young, and positively correlated with memory performance in older participants, both before and after controlling for head motion. Thus, in regard to the relationships between cortical thickness, age and cognitive performance, our results are consistent with previous findings, and were not altered by controlling for head motion. The current study further demonstrated an age-dependent relationship between head motion and memory performance, which was reliable in the two younger groups only. We conjecture that the latter correlation is mediated by factors, such as cognitive control, that relates to both a propensity for movement in the scanner as well as poorer memory performance. In the older participants, we suggest that such a relationship may have been diluted by non-cognitive factors that also influenced amount of motion.

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**Program#/Poster#:** 526.04/VV19

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIA Grant AG039103

Ruth L. Kirschstein National Research Service Award AG049583

**Title:** Age differences in pre-stimulus subsequent memory effects: A time-frequency analysis

**Authors:** ***N. HAUCK**, J. KOEN, E. HORNE, M. RUGG
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**Abstract:** Pre-stimulus subsequent memory effects (preSMEs) - differences in neuronal activity immediately preceding the onset of subsequently remembered and forgotten events during encoding - are thought to reflect proactive processes that benefit memory encoding. A recent study from our lab found differences between young and older adults in preSMEs assessed with event-related potentials (ERPs). Specifically, young adults showed preSMEs during the second or so prior to the onset of a to-be-remember stimulus, whereas older adults did not. The purpose of the current study was to examine if there are age differences in preSMEs using time frequency analysis of these EEG data. In this study, 24 healthy young and older adults studied words for a subsequent memory test. A task cue, that onset 2000 ms before each word, signaled one of two semantic judgments (shoebox or manmade) to perform on the word. Participants were then presented with the word for either a short (300 ms) or long (1000 ms) duration. The goal of this manipulation was to place differential demands on preparatory processes initiated by the onset of the task cue. Memory for the words was tested some 10 minutes after the study phase. EEG data from the pre-stimulus period (locked to the onset of the task cue) was subjected to time frequency analysis using Morlet wavelets from 4-20 Hz (7 cycles per wavelet), and the present analysis focused on three frequency bands: theta (4-7 Hz), alpha (8-12 Hz), and low beta (13-20 Hz). In the young adults, power increases in theta were associated with successful subsequent memory performance in the short encoding condition only, whereas theta was not modulated by subsequent memory in older adults or in the long encoding condition in young adults. Additionally, power in the low beta frequency range differed according to the accuracy of a subsequent source memory judgment undertaken on the words. This effect occurred quite early in the pre-stimulus epoch and was age-invariant. These results largely mirror those from the ERP

analyses, and suggest that young and older adults differ, at least in some respects, in how they engage preparatory processes to benefit memory encoding.

**Disclosures:** **N. Hauck:** None. **J. Koen:** None. **E. Horne:** None. **M. Rugg:** None.

**Poster**

**526. Aging and Memory**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 526.05/VV20

**Topic:** H.02. Human Cognition and Behavior

**Support:** Fondation de l'Université

**Title:** Can spontaneous EEG activity predict spatial working memory performance during normal aging in humans?

**Authors: *G. KLENCKLEN**, A. JABÈS, P. BANTA LAVENEX, P. LAVENEX
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**Abstract:** Normal aging is associated with numerous cognitive changes, including an overall decline in working memory performance. Whereas some neuropsychological evaluations have suggested that visuo-spatial working memory may exhibit a greater age-related decline than verbal working memory, we have previously shown that age-related declines in working memory performance may be most influenced by the representational demands of the task and its dependence on hippocampal function, and not by the type of information to be remembered. Here, we aimed to determine whether spontaneous brain activity may correlate with, and thus be used to predict, working memory performance during normal aging. We first recorded eyes-closed spontaneous electroencephalographic (EEG) activity in young (20-30 years) and older (65-75 years) healthy adults. We then tested the same subjects in a real-world laboratory memory task to assess their allocentric spatial working memory performance. We found that about 50% of older individuals performed as well as young adults, whereas 50% of older individuals exhibited decreased spatial working memory performance. Preliminary analyses of spontaneous EEG activity revealed some age-related changes consistent with previous findings reported in the literature, in particular a decrease in alpha averaged peak frequencies with age. In addition, spontaneous alpha averaged peak frequencies correlated with spatial working memory performance across age groups. We will present the results of more detailed analyses, including microstates analyses, and discuss whether specific patterns of spontaneous EEG activity may serve as a biomarker associated with memory performance during normal aging.

**Disclosures:** **G. Klencklen:** None. **A. Jabès:** None. **P. Banta Lavenex:** None. **P. Lavenex:** None.

**Poster**

**526. Aging and Memory**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant 1R56AG049793-01A1

**Title:** Age-related changes in resolving proactive interference in associative memory

**Authors: *B. CORBETT**[1], S. M. POLYN[2], A. DUARTE[1]
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**Abstract:** Proactive interference can impair our memory in daily tasks such as retrieving a recently updated email password or the updated dosage of a medication. Existing evidence is mixed with regard to whether older adults are less able to overcome proactive interference in associative memory than younger adults. In the current study, we investigated the effect of varying levels of proactive interference on the degree of episodic precision during associative memory retrieval in young and older adults. In an fMRI paradigm, participants were asked to remember which associate (face or scene) objects were paired with most recently under conditions of high, low or no interference. Following scanning, we tested participants' memory for varying levels of episodic detail about the pairings (i.e. face category vs. gender vs. specific face). Behavioral results show that as proactive interference increased, associative memory performance worsened similarly across groups. Importantly, proactive interference disproportionately impaired older adults' memory for specific, but not general, details about pairs. Imaging results demonstrate that separate PFC processes along the caudal-rostral axis support interference resolution during associative memory retrieval. These results shed light on the conditions under which older adults' associative memory performance will be most impaired and the cognitive control operations that are needed to overcome them.

**Disclosures: B. Corbett:** None. **S.M. Polyn:** None. **A. Duarte:** None.

**Poster**

**526. Aging and Memory**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** CIHR Operating Grant No. 126105

ASRP Grant No. 1435

Hugh E. Burke Fellowship, McGill Faculty of Medicine

**Title:** Differences in prefrontal and hippocampal functional connectivity related to spatial memory performance across the adult lifespan

**Authors: *E. ANKUDOWICH**[1,3], S. PASVANIS[3], M. N. RAJAH[2,3]
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**Abstract:** Reductions in memory for the contextual details of items or events (i.e., context memory) have been found to occur across the adult lifespan from midlife into older adulthood. These context memory deficits are thought to be due, in part, to age-related differences in lateral prefrontal (PFC) and medial temporal (MTL) cortical function. However, there is growing consensus that cognitive abilities such as context memory are mediated by interactive, dynamic functional connections between specialized brain regions. It is therefore possible that age-related differences in the functional connectivity of PFC and MTL regions impact successful context memory and contribute to declines in performance observed with advancing age. The current study aimed to investigate differences in patterns of lateral prefrontal and hippocampal connectivity related to context memory accuracy across the adult lifespan. Using functional magnetic resonance imaging (fMRI), we tested young (20-35; n=44), middle-aged (40-58; n=38), and older (60-76; n=44) adults on memory for the spatial details of photographs of faces. Participants completed both easy (6 faces encoded) and difficult (12 faces encoded) versions of the task. Behaviorally, a Difficulty (easy, hard) x Group (young, middle-aged, older) ANOVA yielded a significant Difficulty x Group interaction on retrieval accuracy ($p<.05$). Although young adults outperformed older adults on both the easy and hard levels of task difficulty, they only outperformed middle-aged adults on the harder task. In addition, middle-aged adults performed no differently from older adults on either level of task difficulty. To assess PFC and MTL connectivity, we used multivariate seed-based partial least squares (seed PLS) to analyze the fMRI data. Extracted activation from a voxel in right dorsolateral PFC and from a voxel in left hippocampus was entered, along with retrieval accuracy, into the PLS analysis to identify whole-brain patterns of correlated fMRI activity in young, middle-aged, and older groups. We found that dorsolateral PFC and hippocampal correlations differentially associated with spatial memory accuracy in young adults relative to middle-aged and older adults. We also found that this pattern interacted with task difficulty. Our results suggest that differences in prefrontal and hippocampal functional connections that contribute to context memory performance may be evident by midlife.

**Disclosures: E. Ankudowich:** None. **S. Pasvanis:** None. **M.N. Rajah:** None.

**Poster**

**526. Aging and Memory**

**Location:** Halls A-C

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**Program#/Poster#:** 526.08/VV23

**Topic:** H.02. Human Cognition and Behavior

**Title:** Aging effects on object and scene mnemonic discrimination in a large-scale adult lifespan approach

**Authors: *J. GÜSTEN**, D. BERRON, E. DUZEL
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**Abstract:** There are distinct neural pathways subserving memory-guided behavior, such as mnemonic discrimination, with item/object memory depending more strongly on perirhinal cortex (PRC) and lateral entorhinal cortex (LEC), while scene/context memory mainly involves a network of parahippocampal cortex (PHC), medial entorhinal cortex (MEC) and retrosplenial cortex (RSC)(Ranganath&Ritchey, 2012). Aging affects these domain-specific pathways in a differential fashion but it remains unclear whether that results in differential and domain-specific memory impairments across the adult lifespan. In this study, we investigate ageing effects on object vs. scene mnemonic discrimination across the entire adult lifespan. 2000 adult participants (age range 18-79 years) performed a computerized object-scene mnemonic discrimination task (Berron et al., in preparation). Participants were recruited online via the crowdsourcing platform Amazon Mechanical Turk (AMT), which has shown to be a promising and increasingly used tool for behavioral psychological research (Crump et al., 2013). Each participant was tested for 25 minutes on a subset of 1194 stimulus pairs, consisting of 610 object pairs and 584 scene pairs. Object and scene pairs were presented in a 2-back task design. Participants had to indicate whether a stimulus was repeated identically (repeat) or presented in a similar version (lure) via button presses. We found evidence that ageing affects memory for objects and scenes differentially across the adult lifespan and that object and scene performance become more independent from each other with age. These results are important for future research to better understand how these distinct memory processes are affected in ageing and disease, and to apply behavioral paradigms as non-invasive tools to detect early changes in cognitive functioning.

**Disclosures: J. Güsten:** None. **D. Berron:** None. **E. Duzel:** None.

**Poster**

**526. Aging and Memory**

**Location:** Halls A-C

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant AG034613

**Title:** Age-related deficits in the mnemonic similarity task for objects and scenes

**Authors: *S. M. STARK**[1], C. E. STARK[2]
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**Abstract:** Using the Mnemonic Similarity Task (MST), we have demonstrated an age-related impairment in lure discrimination, or the ability to recognize an item as distinct from one that was similar, but not identical to one viewed earlier. A growing body of evidence links these behavioral changes to age-related alterations in the hippocampus. In this study, we sought to evaluate a novel version of this task, utilizing scenes that might emphasize the role of the hippocampus in contextual and spatial processing. In addition, we evaluated differential contributions to these tasks by relating performance on objects versus scenes to volumes of the hippocampus and surrounding medial temporal lobe structure. We collected behavioral data on the objects and scenes task in a group of 26 younger (ages 21-38 years old) and 28 older (59-84 years old) adults, in addition to structural MRI scans. We found that while there was an age-related impairment in lure discrimination for both objects and scenes, relationships to brain volumes and other measure of memory performance were stronger when using objects. In particular, lure discrimination performance for objects showed a positive relationship with the volume of the hippocampus, specifically the combined dentate gyrus and CA3 subfields and the subiculum. Further, we found that four measures of memory performance (MST-Objects LDI, MST-Scenes LDI, RAVLT delay, and Rey-O delay) were strongly related and dependent on the hippocampus and surrounding MTL cortices, relationships that were maintained even when age was regressed out of the relationships. In conclusion, we found little evidence to support a benefit to using scenes over objects in the MST. While both tasks resulted in an age-related decline in lure discrimination performance, relationships with hippocampal and MTL volumes were much stronger for MST-Objects. Likewise, Objects LDI showed a stronger relationship with standardized measures of memory (RAVLT and Rey-O delayed recall). Our data also suggests that the Rey-O may be a stronger measure of memory and possibly less prone to non-memory strategy that would alter performance, though that is partly speculation on our part. In conclusion, these findings emphasize the utility of MST-Object lure discrimination in revealing age-related memory changes and the relationship to hippocampal circuit alterations.

**Disclosures:** **S.M. Stark:** None. **C.E. Stark:** None.

**Poster**

**526. Aging and Memory**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 526.10/VV25

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Hungarian National Brain Research Program (NAP), contract# KTIA_NAP_13-2014-0015

**Title:** Establishing a new skill learning model, "pot-jumping" in rats

**Authors: *A. J. ERNYEI**[1,2], T. GROHMANN PEREIRA[1], K. KOZMA[1,2], F. KASSAI[1,2], I. GYERTYÁN[1,2]
[1]MTA-SE NAP B Cognitive Translational Behavioural Pharmacol. Group, Semmelweis University, Dept. of Pharmacol., Budapest, Hungary; [2]Inst. of Cognitive Neurosci. and Psychology, Res. Ctr. for Natural Sci. - MTA, Budapest, Hungary

**Abstract:** Impairment of procedural memory is a frequent and severe symptom in many neurological and psychiatric diseases as well as during aging. Our aim was to establish an assay in rats in which procedural learning and changes in performance can be studied on long-term. The work was done in the frame of a larger project aiming to establish a complex cognitive animal test battery of high translational value.
Subjects of the study were 36-36 male 5 months old Lister-Hooded (LH) and Long-Evans (LE) rats kept on reversed light-dark cycle and restricted food-access. Parallel to the pot-jumping training the animals participated in various other cognitive tasks. The equipment was a 190 cm diameter circular open arena with 60 cm high walls where 12 flower pots (16 cm high, 10 and 17.5 cm wide at base and top, respectively) were placed upside down in a circle form with increasing distances (18-46 cm) between them. The arena was filled 6 cm deep with cold water to make the rats refrain from descending from the pots. An animal was put onto the start pot (the one within the shortest distance to the next) and allowed to move on the pots for 3 min. Training sessions were held at least once a month. Movement of the animals were video-recorded.
Motor skill development was characterized by the longest distance successfully spanned by the rats across all the trials. They were able to step over from one pot to the other until 26 cm distance, but had to jump beyond 26 cm. The distribution of the “personal best” values of LE animals showed a more or less Gaussian curve between distances of 24 and 40 cm with a mode of 34 cm (11 rats). In contrast, the distribution of LH rats was uniform spreading from 24 to 46 cm. There were 4 LE and 8 LH animals which did not move longer than 26 cm. The “record” of LE rats was 40 cm jumped by 4 animals, while 7 LH rats could reach the 44 cm range, and the recorder jumped even 46 cm. A relatively flat bell-shaped age-dependence was observed; the

mean longest distance peaked around the age of one year both in LE and LH rats (32.8 and 37.0 cm, respectively).
Animals were obviously motivated to move around on the pots, however, the distance which required jumping meant a barrier for some of them. The LH group involved more courageous as well as more anxious rats than the LE cohort. A slow decline in performance could be observed after the age of 2 years which might be connected to decreased motivation and/or motor coordination ability.
The study was funded by the Hungarian National Brain Research Program (NAP), contract# KTIA_NAP_13-2014-0015.

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**Poster**

**527. Cognitive Aging**

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**Program#/Poster#:** 527.01/VV26

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH/NIA R01 AG26158

**Title:** White matter tracts mediate age-related cognitive inhibition decline in Stroop interference

**Authors: *P. LI**, Y. GAZES
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**Abstract:** One potential source of the age-related decline in cognitive inhibition is the integrity of the underlying white matter. Previous DTI studies have found associations between white matter integrity and performance on the Stroop test. The current study aimed to add to these studies of cognitive inhibition by investigating how the differences in age and in white matter integrity relate to Stroop performance, and to examine whether the effect of age on Stroop performance is mediated by white matter integrity. Method:179 healthy adults from 20-80 years old were recruited in the study. DTI data were processed through TRACULA and the mean fractional anisotropy (FA) of 18 major white matter tracts were extracted and used for statistical analysis. Correlation analysis was performed to examine the relationship between age and the Stroop interference score (IG). Simple linear regressions were performed between the mean FA and age to investigate if age is a predictor of FA, and between FA and IG to examine if FA is a predictor of IG. For significant results exceeding the multiple comparison correction, a moderation analysis was performed to examine if there is an interaction effect of age and FA on IG. Finally, for those that we did not find a moderation effect, we investigated if FA mediated the effect of age on IG. Results: Correlation analysis showed a strong negative relationship

between age and IG. Higher IG indicated better cognitive inhibition. Simple linear regression analyses indicated that most of the tracts showed negative relationships with age, and positive relationships with IG. Moderation effect of age on the relationship between FA and IG was tested on tracts that significantly predicted IG after multiple comparison corrections, but none of these moderations were significant. Then we tested if these tracts mediated the effect of age on IG and found significant indirect effects of age on IG through the FA of the left corticospinal tract and through the right inferior longitudinal fasciculus. In both mediation results, age was negatively associated with FA, consistent with the decline in white mater integrity in older age, and the FA was positively associated with IG,demonstrating better inhibitory performance with more intact white matter integrity.Conclusions: Our results highlight the role of a number of major white matter tracts in the processes supporting the Stroop inhibitory performance and further pinpointed the lower white matter integrity of the inferior longitudinal fasciculus and the corticospinal tract as contributors to the decrease in inhibitory ability associated with the Stroop test in older age.

**Disclosures: P. Li:** None. **Y. Gazes:** None.

**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant R01AG026458-09

NIH Grant R01AG038465-06

**Title:** Age and education have fundamentally different multimodal neural substrates than verbal intelligence across the life span

**Authors: *C. G. HABECK**[1], Q. R. RAZLIGHI[2], Y. GAZES[1], Y. STERN[3]
[1]Taub Inst., [2]Neurol., Columbia Univ., New York, NY; [3]Cognitive Neurosience Division, Columbia Univ., New York, NY

**Abstract:** We conducted a multimodal investigation to what extent the formative factors education and biological age influence people’s structural and functional brains, and lead to different neural correlates from the reflective factor verbal intelligence, operationalized as NARTIQ. We analyzed a cross-sectional multi-modal data set which consisted of (1) structural data (=cortical thickness in 68 ROIs) and (2) resting-state functional-connectivity data (=264 x 264 temporal correlation matrices) for 451 participants, and (3) fMRI-activation data from 12 cognitive tasks for 255 participants. To assess the influence of age, education and verbal

intelligence, we picked all possible pairs of participants who differed in all three factors by less than the pre-specified upper bounds ΔEducation, ΔAge and ΔNARTIQ. The stringency of the matching requirement was varied systematically to verify that the results of the performed analyses behaved in a consistent manner. We computed pair-wise similarities for all neuroimaging data modalities, i.e. for any participant-pair conforming to the matching requirements we computed the topographic correlation between the neural data from both participants in the pair. For cortical thickness, this entailed a correlation across all 68 ROIs between both participants' thickness data. For resting-state connectivity, it entailed a correlation between all off-diagonal elements of the 264 x 264 connectivity matrices of both participants. Lastly, for functional activation, it entailed the correlation across all voxels between both participants' functional-activation maps. The correlations were Fisher-Z transformed and then served as dependent variables in a linear regression, where the average values of age, education and NARTIQ of the corresponding participant pairs were used as simultaneous independent variables. Despite variations in statistical significance, a consistent finding emerged for all modalities: similarity of thickness, resting connectivity and functional activation between two participants was associated *negatively* with age and education, but *positively* with NARTIQ. Age and education, when carefully matched, might induce changes in participants' brains that become greater with the level of age or education. NARTIQ, on the other hand, seems to capture latent and innate neural factors that cause participants' brains to be more similar with higher levels. These findings point to fundamental differences in the neural substrates of formative and reflective subject variables, and caution against combining such variables into composites for the purpose of mapping unidimensional neural substrates.

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**Poster**

**527. Cognitive Aging**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant K01AG051777

**Title:** Application of awFC, a technique combining functional and structural connectivity, in the context of aging and a reasoning task performance

**Authors: *Y. GAZES**[1], D. F. DRAKE[2], F. D. BOWMAN[2]
[1]Taub Inst., [2]Columbia Univ., New York, NY

**Abstract:** Both functional and structural connectivity in brain networks are predictive of cognitive decline in aging, but more robust networks can be identified if structural connectivity

information is incorporated into the network analysis. Our study used the Anatomically Weighted Functional Connectivity analysis (awFC) (Bowman, 2012) to identify brain networks involved in performing a reasoning task called the Letter Set task, a reasoning task, in a group of 78 older adults (mean age=69.2±5.54 years old). Functional Magnetic Resonance Imaging (fMRI) data were collected during the performance of the Letter Set task and was analyzed in FSL to get the set of regions associated with task performance. Tractography was performed on Diffusion Tensor Imaging (DTI) data also using FSL for 90 regions of interest from the AAL templates, from which structural connectivity was calculated and used as weights for evaluating functional connectivity among the ROIs. Results: Mean task accuracy was .689±.224 and the median RT was 15.9±6.7 s. All age effects were negative such that older age was associated with lower connectivity strength and the strongest Age effect was observed in the connections between the right calcarine and the right inferior temporal gyrus ($z = -3.1$, $p=.0017$). For task accuracy, both positive and negative relationships were observed, suggesting that stronger connection between some regions pairs are beneficial for task performance while others are detrimental to task performance. The strongest positive relationship was observed between the right inferior parietal lobule and the left angular gyrus ($z=3.05$, $p=.002$), whereas the strongest negative relationship was observed between the right postcentral gyrus and the left paracentral lobule ($z=-3.3$, $p=.0009$). A positive Age by Task accuracy interaction was also found such that the older and higher performance subjects showed stronger connections between region pairs. The region pair with the stronger interaction effect was between the left middle occipital gyrus and the left inferior temporal lobule ($z = 3.2$, $p = .0015$). The results are consistent with the theory that cognitive decline in aging is associated with disconnected brain regions. Furthermore, high performers among older adults showed stronger connections among region pairs.

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**Poster**

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McKnight Brain Research Foundation

State of Arizona and Arizona DHS

**Title:** Regional covariance patterns of white matter microstructure in healthy aging

**Authors: *L. A. NGUYEN**[1,2,3], P. K. BHARADWAJ[1,2,3], M. C. FITZHUGH[1,2,3], K. A. HAWS[1,2,3], G. A. HISHAW[4], J. R. MOELLER[8], C. G. HABECK[9], T. P. TROUARD[5], G. E. ALEXANDER[1,2,3,6,7]
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**Abstract:** Diffusion tensor imaging (DTI), a non-invasive method for characterizing microstructural white matter, has been used to evaluate white matter differences in aging. Previous studies have primarily applied univariate approaches for evaluating relations between age and DTI metrics of white matter integrity, with prominent results showing associations between advancing age and decreases in fractional anisotropy (FA) and increases in mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). We applied a multivariate method, the Scaled Subprofile Model (SSM; Alexander & Moeller, 1994), to identify separate white matter regional network patterns for each diffusivity measure that optimally predicted age in a sample of 196 neurologically healthy community-dwelling older adults, ages 50-89. Additionally, we assessed the contributions of common vascular risk factors, including white matter hyperintensities (WMH), hypertension, and homocysteine, to each covariance pattern. We used TRACULA for automated probabilistic tractography to reconstruct 18 major white matter pathways and to generate estimates of FA, MD, RD, and AD. We used a multivariate model of regional network covariance, SSM, to identify regional patterns of white matter integrity associated with aging. We found distinct age-related regional patterns of white matter tracts for each diffusivity metric ($5.3E\text{-}9 \leq p \leq 0.001$). Additionally, there were no interactive effects of vascular risk factors and age on the covariance patterns. Only WMH volume showed an additive effect on the white matter integrity network patterns for FA, MD, and AD ($0.019 \leq p \leq 0.029$), whereas hypertension and homocysteine did not show contributory effects. Together, these findings suggest that in the context of healthy aging, damage to white matter microstructural tracts may differentially predict advancing age through region-specific effects and may be further influenced by macrostructural white matter lesion load.

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**Poster**

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McKnight Brain Research Foundation

State of Arizona and Arizona DHS

**Title:** Multimodal neuroimaging reveals white matter microstructure related covariance networks of subcortical gray matter volumes in healthy aging

**Authors: *P. K. BHARADWAJ**[1,2], M. C. FITZHUGH[1], L. A. NGUYEN[1,2], K. A. HAWS[1], G. A. HISHAW[3], T. P. TROUARD[4], J. R. MOELLER[7], C. G. HABECK[8], G. E. ALEXANDER[1,2,5,6,9]
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**Abstract:** Healthy aging preferentially affects selected gray matter (GM) and white matter (WM) brain regions and has been widely studied using univariate analysis methods. Multivariate network analysis of multimodal magnetic resonance imaging (MRI) data may potentially improve regional characterization of age-related differences by combining information from complementary imaging modalities. Here we use this framework to investigate how differences in global WM microstructural integrity relate to regional network covariance of subcortical grey matter (SGM) volumes, including the hippocampus, amygdala, thalamus, pallidum, putamen, caudate and nucleus accumbens, and further assess how this pattern is related to age and regional white matter hyperintensity (WMH) load. T1-weighted volumetric, diffusion weighted imaging (DWI), and T2 FLAIR 3T MRI scans were obtained in 196 healthy community dwelling older adults, 50 - 89 years of age (mean±sd age = 69.8 ± 10.6; 95F/101M). Freesurfer v5.3 was used for segmenting T1 scans and extracting SGM volumes. DWI scans were processed with TRACULA and global fractional anisotropy (FA) and mean diffusivity (MD) were computed as the average of 18 major WM tracts. WMH maps were produced by automated multispectral

segmentation using SPM12's Lesion Segmentation Toolbox. A lobar atlas template was used to obtain regional WMH volumes from the four major lobes. The Scaled Subprofile Model was applied to the SGM volumes to derive their regional covariance networks in relation to global mean FA and MD. The FA-related SGM network pattern accounted for 9.8% of the variance in FA, included relative reductions in bilateral thalamus with preservation of the right caudate, but was not related to age ($p = 0.73$). The MD-related SGM network pattern accounted for 18.6% of the variance in MD, exhibited volume reductions bilaterally in hippocampus and putamen with relative preservation of left caudate and right pallidum, and was positively related to age ($r^2 = 0.29$, $p = 1.1E-16$). After adjusting for age, gender, years of education and hypertension status, the FA-SGM pattern was not related to regional WMH (FDR $p > 0.14$), while the MD-SGM pattern was positively related to WMH load in the frontal ($r^2 = 0.078$, FDR $p = 9.0E-6$), temporal ($r^2 = 0.06$, FDR $p = 7.5E-5$) and parietal ($r^2 = 0.045$, FDR $p = 4.9E-4$) lobes. Together, these findings demonstrate the regionally varying impacts of differential aspects of WM integrity on subcortical GM in the context of healthy aging, providing further support for using multimodal, multivariate network analyses to more fully characterize the regionally distributed effects of brain aging.

**Disclosures: P.K. Bharadwaj:** None. **M.C. Fitzhugh:** None. **L.A. Nguyen:** None. **K.A. Haws:** None. **G.A. Hishaw:** None. **T.P. Trouard:** None. **J.R. Moeller:** None. **C.G. Habeck:** None. **G.E. Alexander:** None.

**Poster**

**527. Cognitive Aging**

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**Topic:** H.02. Human Cognition and Behavior

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McKnight Brain Research Foundation

State of Arizona and Arizona DHS

**Title:** Network covariance of hippocampal subfield volumes associated with healthy aging and the risk for Alzheimer's disease

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**Abstract:** It is well established that healthy aging is associated with regional brain atrophy, which may be exacerbated by an increased risk for Alzheimer's disease (AD) with the apolipoprotein E (APOE) ε4 allele. We have previously reported regionally distributed network patterns of gray matter volume throughout the brain associated with healthy aging and APOE risk for AD (Alexander et al., 2006, 2012; Bergfield et al., 2010) using magnetic resonance imaging (MRI) and a multivariate model of regional covariance, the Scaled Subprofile Model (SSM; Alexander and Moeller, 1994). In this study, we sought to evaluate the effect of aging on the SSM network pattern of hippocampal subfield volumes in a cohort of healthy, community-dwelling middle-aged to older adults, who were screened to exclude common medical conditions of aging, including hypertension and diabetes. T1-weighted 3T volumetric MRIs were obtained in 81 healthy adults (45F/36M, mean±sd age = 66.2±10.1, mean±sd Mini-Mental State Exam = 29.2±0.9, APOE ε4 status = 22 carriers/59 non-carriers), 50 to 89 years of age. Image processing was performed using Freesurfer (v6.0) software to obtain bilateral hippocampal sub-region volumes of CA1, CA3, CA4, dentate gyrus granule cells (DG-GC), molecular layer, subiculum, presubiculum, and hippocampal tail. Total intracranial volume (TIV) was computed for each participant's native scan using SPM12. Regional network analysis was performed with SSM bootstrap re-sampling and 10,000 iterations on the TIV-adjusted hippocampal subfield volumes using the Akaike information criterion. A linear combination of the first eight SSM components was associated with increasing age in the sample ($R^2 = 0.27$, $p \leq 2.49E\text{-}3$). This regional pattern was characterized by volume reductions in bilateral DG-GC and molecular layer sub-regions with relative increases in bilateral CA3. Univariate regional analyses showed that each of the bilateral DG-GC and molecular layer sub-regions were inversely correlated with age ($p's \leq 2.86E\text{-}5$), whereas CA3 regions did not reach significance ($p's \geq 0.07$). After we controlled for age and gender, expression of the SSM pattern was greater in the APOE ε4 carriers than non-carriers ($p \leq 0.004$). The results indicate a regionally specific pattern of hippocampal subfield volumes with reductions in the vicinity of the dentate gyrus and relative preservation in the region of CA3 that is associated with healthy aging, and is further expressed to a greater extent in APOE ε4 carriers. Together, these findings support selective regional vulnerability of the dentate gyrus in the context of healthy aging and in relation to genetic risk for late onset AD.

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**Poster**

**527. Cognitive Aging**

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**Topic:** H.02. Human Cognition and Behavior

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McKnight Brain Research Foundation

State of Arizona and Arizona DHS

**Title:** Relation of physical sport activity to regional white matter integrity in older adults

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**Abstract:** Physical activity (PA) may have an important role in maintaining cerebral white matter (WM) integrity in healthy aging. We sought to determine whether high levels of self-reported physical sport activity are associated with better WM integrity. Self-report ratings of physical sport activity were obtained from 210 healthy older adults (M ± SD age = 70.0 ± 10.4 yrs). Participants reporting high sport activity (n=38) were compared to those with low sport activity (n=172). T1 and diffusion weighted 3T MRIs were processed using Freesurfer v5.3 and TRACULA for tractography to compute fractional anisotropy (FA) and mean (MD), radial (RD), and axial (AD) diffusivity for 18 WM tracts. ANCOVA tested age group (young-old group (YO) = 50-69 yrs; old-old group (OO) = 70-89 yrs), PA group, and interaction effects after controlling for hypertension status. No main effects for PA group ($p$'s > 0.05) were observed across all four diffusion metrics. For FA, results revealed main effects for age group for three WM tracts ($0.003 \leq p \leq 0.006$) such that, for two tracts, the OO had lower values. All age group effects for MD, RD, and AD revealed that the OO had higher diffusion than the YO. For MD, we found age effects for all but one bilateral WM tract ($2.0E\text{-}5 \leq p \leq 0.039$). For RD, we found age effects for all but one bilateral and two individual WM tracts ($0.002 \leq p \leq 0.048$). For AD, effects for all but two bilateral and two individual WM tracts ($4.0E\text{-}7 \leq p \leq 0.047$) were observed. We found age

by PA interactions for two tracts for FA, left inf. longitudinal fasciculus (ILF; $p = 0.045$) and right uncinate (UNC; $p = 0.025$). Interactions were observed for the same three tracts, ant. thalamic radiation (ATR), sup. longitudinal fasciculus-parietal (SLFP), and temporal (SLFT) bundles, bilaterally for MD ($0.016 \leq p \leq 0.04$) and in left tracts of AD ($0.007 \leq p \leq 0.037$). An interaction was observed for left ILF for MD ($p = 0.011$) and right cingulum cingulate gyrus (CCG) for AD ($p = 0.035$). For RD, interactions were observed for bilateral SLFT, left ILF, right ATR, SLFP, and UNC ($0.007 \leq p$'s $\leq 0.043$). Simple effect analyses showed that within the OO, those with lower PA had lower FA for the ILF tract ($p = 0.011$). For the UNC tract, among those with low PA, the OO had lower FA ($p = 0.012$). Effects for MD, RD, and AD showed that among those with low PA, the OO had higher diffusion ($p \leq 0.002$). In the OO, those with low PA had higher diffusion in all but one tract for MD and RD and two tracts for AD ($0.002 \leq p$'s $\leq 0.043$). After adding gender as an additional covariate for main and interaction effects, the regional findings were consistent. These findings suggest that high levels of PA may be an important lifestyle factor that can help to maintain WM integrity in old age.

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**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 527.08/VV33

**Topic:** H.02. Human Cognition and Behavior

**Title:** The role of anxiety on the cognitive control of gait in older adults

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**Abstract:** Falls are a prevalent and significant problem in older adults. Fear of falling in older adults has been associated with an increased fall risk and decreased quality of life and active participation. Based on the attentional control theory, anxiety is posited to impair processing efficiency to a greater extent than performance on tasks that involve the central executive. Given the importance of attention on the cognitive control of gait in older adults, we hypothesize that increasing anxiety due to walking on a virtual beam, will result in a decreased efficiency of activation of the prefrontal cortex (PFC) in older adults. Using a combination of functional near-infrared spectroscopy (fNIRS) with virtual reality, we examine changes in PFC activity while walking in healthy young (HYA, n=10) and older adults (HOA, n=12). Participants were asked to walk at a comfortable pace on an instrumented treadmill. While walking, simultaneous fNIRS and force plate data from the instrumented treadmill was collected. Using a self-paced gait,

participants were presented with either no visual stimuli (NW = normal walking) or with a narrow virtual reality beam (BW = virtual beam walking), so as to elevate anxiety. In all conditions, participants walked for 75 seconds, with 30 seconds to warm-up, 30 seconds for steady state walking, and 15 seconds to cool-down. Prior to each task, a 10 second baseline was collected for data analysis. Measures collected included spatiotemporal gait parameters (i.e., stride length and stride time) and PFC activation levels, evaluated by oxygenated hemoglobin (HbO2) levels. The effect of group (HYA vs. HOA) and task (NW vs. BW) on outcome measures was evaluated using linear mixed models, with intercepts for individuals modeled as a random effect. Significance was set at $p = .05$, using R 3.1.1. Overall, a significant interaction between age and task ($p < .05$) was observed on stride length and stride time. In addition, the task resulted in significant changes in stride length and stride time ($p < .05$). In older adults, a significant increase in PFC oxygenation levels was observed in BW relative to NW ($p < .05$). The increases in HbO2 levels observed from NW to BW suggest that increased attention is necessary for walking on a virtual beam relative to normal walking, consistent with the attentional control theory. Future studies should examine a larger sample of individuals with and without fall-related anxiety and explore the relationship between anxiety, attention, and cognitive control of gait in older adults.

**Disclosures:** **M.E. Hernandez:** None. **M.E. Kersh:** None. **G. Chaparro:** None.

**Poster**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** Heart and Stroke Foundation Doctoral Award

Ontario Graduate Scholarship

**Title:** Default to executive coupling is associated with divergent thinking in older adulthood

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**Abstract: Introduction:** The default – executive coupling hypothesis of aging (DECHA) posits that increased functional coupling between the default network (DN) and executive control regions occurs in response to increased cognitive control demands in older adulthood (Turner and Spreng, 2015). A similar pattern of network coupling has been associated with divergent

thinking (DT) and creativity in young adults, possibly reflecting flexible engagement of control and associative processes (Beaty et al., 2015). Divergent thinking and creative ability remains constant across the adult lifespan (e.g. Addis et al., 2016; Palmiero et al., 2014; Roscos-Ewoldson et al., 2008). This suggests that default – executive coupling may support divergent thinking in the context of declining cognitive control capacity in later life. However, this has not been directly investigated.
**Methods:** Young (N=30) and Old (N=25) adults completed a divergent thinking (alternate uses) task while undergoing fMRI scanning. Functional connectivity analyses were conducted using the Conn Toolbox. DMN and executive control regions were defined a priori from a functional cortical parcellation scheme (Gordon et al., 2014). Age-related differences in functional connectivity within the DN, and between default and executive control regions, were contrasted across the Control and DT conditions. **Results:** Age-related increases in functional connectivity within the DN were observed during the DT but not the Control condition. Specifically, increased functional connectivity was observed between left posterior superior temporal gyrus and right medial PFC, right medial superior frontal gyrus and the posterior cingulate cortex and anterior medial PFC. Consistent with the DECHA, age-related increases in functional connectivity during DT was observed between left dorsolateral PFC and the DN (left posterior cingulate cortex, anterior medial PFC and angular gyrus).
**Conclusions:** Our results provide early evidence for age-related increases in connectivity within the DN and between default and executive control regions during creative thought, consistent with DECHA. While speculative, this may reflect greater reliance on associative processing (mediated by DN regions) in the context of declining cognitive control in older age. DECHA has been associated with age-related decline in fluid reasoning ability (e.g. Rieck et al., 2017). However, in the domain of creative thought, where past knowledge and experience may provide access to a larger solution space, such brain changes may be adaptive. These data identify DECHA as putative neural mechanism supporting creative thinking across the adult lifespan.

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**Poster**

**527. Cognitive Aging**

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**Program#/Poster#:** 527.10/VV35

**Topic:** H.02. Human Cognition and Behavior

**Title:** Factors associated with daytime sleepiness in older adult

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**Abstract:** Introduction: Daytime Sleepiness (DS) may be considered a symptom or risk factor associated with sleep disorders and physical or mental illness, and is frequently evaluated using the Epworth Sleepiness Scale (ESS). In older adults, changes are observed in the circadian cycle of sleep and wakefulness, including phase advance and decrease in total sleep time. Objective: The objective of this study was to determine the presence of DS in a sample of older adults and its association with demographic and health variables, substance use, and daytime and nocturnal symptoms. Method: Observational, retrospective chart review of patients 60 years and older during 2009-2013 at the Sleep Disorder Clinic of the Faculty of Medicine, National Autonomous University of Mexico. The measures of association used were chi-squared and odds ratios. A multivariate logistic regression was also performed. Results: 53.4% of the population showed DS, and 83% Obstructive Sleep Apnea Syndrome (OSAS). Using odds ratios, a positive association was found between DS and OSAS, nighttime breathing problems, snoring interrupted by silence, use of alcohol to sleep, perceived sleep latency <30 minutes, and napping. A negative association was found between DS and the use of drugs to fall asleep and wake up earlier. The multivariate logistic regression showed a positive association with naps, self-reported somnolence, and OSAS diagnosis. Conclusion: The ESS is a valuable tool for the preliminary diagnosis of OSAS in older adults. Together with other measures, such as body mass index (BMI) and interrupted snoring, it can aid in the timely referral of such patients to confirmatory polysomnography.

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**Poster**

**527. Cognitive Aging**

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**Program#/Poster#:** 527.11/VV36

**Topic:** H.02. Human Cognition and Behavior

**Title:** Modified stroop task-set switching test: Brief screening for executive functioning across the life span

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**Abstract: Background**. The relationship between executive functioning (EF; high-level processes involved in monitoring and controlling goal-directed behavior) and age has shown contradictory findings. Some studies have reported an age-related change in certain EF across the life span whereas others did not. This may result from the lack of neuropsychological tests of EF that are applicable across all life stages. This study sought to address this issue by developing a new neuropsychological test (i.e., Modified Stroop Task-Set Switching; MSTSS) designed to assess four components of EF, namely flexibility, inhibition, working memory updating, and planning. **Objective**: This study aimed at examining the utility of MSTSS in the assessment of EF from childhood to old age, in order to identify the most sensitive measures of early EF decline. **Methods:** A sample of 129 participants ranging in age from 9 to 75 years completed: i) standardized neuropsychological tests (SNT) evaluating flexibility (Trail Making Test), inhibition (Stroop Test), working memory updating (Forward and Backward Digit Span), and planning (Rey Complex Figure), and ii) MSTSS. Principal component analysis and multiple regression analysis were used to demonstrate the utility of MSTSS (i.e., response time and the number of errors in flexibility, inhibition, working memory updating, and planning, respectively) for early detection of age-related EF decline. **Results and discussion:** A U-shaped relationship was found between age and EF, as assessed by both SNT and MSTSS, with larger costs in response time (i.e., time of completion in each test) for children (mean±SD: 10±1 years), middle-aged (50±5 years) and older (66±4 years) adults. Most interestingly, principal component analysis revealed that the response time and the number of errors in MSTSS are more correlated with age than measures from SNT. Specifically, only the number of errors in inhibition (as assessed by MSTSS) was selectively increased in older adults, demonstrating that this measure is more sensitive to age-related change in EF as compared with measures from SNT. Moreover, multiple linear regression showed that measures from SNT could predict response time in MSTSS, suggesting that the latter could be used as a global measure of EF efficiency across the life span. **Conclusions**: The findings demonstrated that MSTSS, and more specifically the number of errors in inhibition, is more sensitive to aging than SNT.

**Disclosures: M. Belghali:** None. **C. chesneau:** None. **D. Davenne:** None.

**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

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**Program#/Poster#:** 527.12/VV37

**Topic:** H.02. Human Cognition and Behavior

**Title:** Structural integrity of the dorsal striatum correlates with learning rate in a valenced go/no-go task

**Authors: *V. PEROSA**[1,2], M. BETTS[1], M. GUITAT-MASIP[3], G. ZIEGLER[1], E. DUEZEL[1,4]
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**Abstract: Background:** Evidence exists showing an association between instrumental learning and the dorsal striatum. In this study we used voxel based morphometry (VBM) to investigate the role of the dorsal striatum in instrumental learning in the healthy ageing brain, using ultra-high resolution magnetic resonance imaging (MRI) at 7 Tesla. **Methods:** We performed a VBM-analysis on T1-weigthed MPRAGE images (0.8 mm iso) using CAT12 (Gaser and Dahnke, 2012) to investigate, whether changes in grey matter (GM) volume in the striatum influenced learning in the ageing brain. We tested 25 young adults (mean age = 24.1, 12 females and 13 males) and 30 community-dwelling elderly adults (mean age = 68.58, 19 females and 12 males). Participants completed a go/no-go behavioral task, which orthogonalizes action (performing an active response or withholding it) and valence outcome (reward or punishment) (Guitart-Masip et al., 2011). A task-specific computational reinforcement learning model was applied to our results and its parameters were implemented in the VBM analysis. **Results:** Behavioral data showed how participants had more difficulties to avoid losing by performing an action and obtaining reward by withholding it, as already descripted in previous studies (Chowdhury et al., 2013; Guitart-masip et al., 2012). Furthermore, performance and learning in older adults was overall poorer, especially in the no-go conditions. After calculating the modelling parameters, an age-related difference was observed in learning rate, reward and punishment sensitivity, which were then included in the VBM-analysis. In a group comparison, we found learning rate in older adults positively correlated with GM volume in bilateral caudate nucleus. An additional multiple regression analysis to assess individual variability in older adults also revealed a positive correlation with learning and bilateral caudate nucleus. **Discussion:** Our results suggest that age-related structural changes in the caudate nucleus can explain individual variability in learning rate in older adults. This conclusion is consistent with other studies, showing a contribution of the dorsomedial striatum to goal-directed behavior.

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**Poster**

**527. Cognitive Aging**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** Anita Kunin Professorship for Women's Healthy Brain Aging (LMJ)

**Title:** Neural network properties as a function of age and apoE genotype

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**Abstract:** Apolipoprotein E (apoE) is a plasma apolipoprotein implicated in various functions related to brain health and disease. In humans, apoE exists in three primary isoforms - E2, E3, and E4 - that differ in terms of structure and function and, consequently, promotion of risk or resilience for various insults and diseases. The E2 and E3 alleles are thought to confer relative superiority over E4 in terms of brain structure and function. In the present study, we evaluated brain function derived from resting state MEG in 165 cognitively healthy (MoCA $\geq$ 26) participants of age range 28-99 y old according to apoE genotype. We analyzed properties of the neural network, including the flexibility and variability of interactions between MEG sensor pairs. Results demonstrated that network flexibility increased from E4 to E2 genotype whereas network variability decreased from E4 to E2 genotype. Plotting network properties by decade and genotype revealed that both network properties were relatively stable up to the 7th decade of life. After that, the network properties differed substantially according to genotype with E2 carriers evidencing healthier network properties than E4 carriers. Results of this study highlight that the effects of apoE on network functions are manifested more clearly with increasing age, even among cognitively healthy individuals.

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**Poster**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** German Federal Ministry of Education and Research (BMBF) Grant, Project: FANS - Pedestrian Assistance System for Older Road Users

**Title:** Peripheral visual perception and motor performance in younger and older adults: A MoBI-study

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**Abstract:** Human experiences and activities are rarely restricted to a single task and therefore associated with several ongoing perceptual and cognitive processes. Especially in older adults effective resource allocations to these parallel processes are crucial as aging is often associated with interdependent compensation mechanisms of age-related cognitive and sensory declines. Everyday tasks like the maintenance of a stable and secure gait can require increased cognitive control leaving fewer resources for concurrent tasks such as scanning the traffic for peripheral approaching cars or the environment for obstacles. Although techniques to record neurophysiological data during realistic locomotion are nowadays possible using Mobile Brain-Body Imaging (MoBI) approaches, the interplay of visual perception and motor performance and the underlying brain dynamics are not yet understood in detail. Therefore, the present study aimed at investigating peripheral visual perception and motor task performance in a dual-task scenario in older and younger adults. Furthermore, the potential of vibro-tactile warning cues to improve the perception of peripheral stimuli in older participants will be evaluated.
A study set-up was realized that allowes for dynamic presentations of visual stimuli at different eccentricities dependent on participants current heading while standing or walking up and down a hallway of ten meter in length. In addition, a device that delivered short vibro-tactile warning cues to the upper arm prior to the visual stimulation was integrated for further assessments. The data recording protocol comprised synchronized recordings of behavioral data, gait and posture parameter and continuous EEG-data by a 64-channel mobile set-up. EEG-, behavioral as well as gait and posture data were yet collected from 15 younger (< 35 years) and 15 older (> 65 years) adults.
The present study results replicate previous findings of dual-task effects on performance measures (response time, errors, misses), as well as posture and gait parameter. Importantly, the EEG data reveal significant differences in stimulus-locked event-related potentials (ERP) between younger and older participants. The study demonstrates the feasibility of MoBI in understanding dual-task effects in young and older adults during naturalistic behavior. The results can be used to design assistance systems for older users in complex traffic situations.

**Disclosures:** **J. Protzak:** None. **K. Gramann:** None.

**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 527.15/VV40

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIA Grant 1R01AG043452

**Title:** Socioemotional and neural correlates of off-task thinking in young and old adults

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**Abstract:** Recent years have brought a growing appreciation that the human mind has a propensity to wander away from the task at hand. Adults spend upwards of half their waking day cognitively disengaged from the here-and-now, yet despite this high frequency, the correlates and consequences of off-task thought are poorly understood. Off-task thought may facilitate problem solving and contribute to one's sense of self-identity, but it can also fuel unhappiness and be associated with psychiatric disorders. Further, little is known about how on- and off-task thoughts change in aging. Despite the well-established cognitive "positivity effect" in old age, the elderly are highly vulnerable to depression and social isolation. These gaps call for a deeper understanding of influences on cognitive and socioemotional well-being across the lifespan. Toward this end, we explored the frequency, content, and correlates of on- and off-task thought in young (N = 42, ages 25-35, mean = 28.5) and older adults (N= 115, ages 60 - 88, mean = 70) across two contexts. First, we developed a trait questionnaire to estimate thought patterns in daily life. Second, we developed a retrospective self-report questionnaire to assess thought content during a 5 minute resting state paradigm while acquiring fMRI data to explore neural correlates of cognitive changes. Results reveal numerous differences between young and older adults, with broad consistency across the two contexts outlined above. Older adults reported less frequent internally-focused off-task thoughts (i.e., mind-wandering), but greater focus on the fixation crosshair and distraction by irrelevant external stimuli. They also displayed greater present-focused and reduced past-focused content, as well as biases toward positive and other-focused thoughts. Among older adults, better well-being was associated with fewer internally-focused off-task thoughts (especially negative thoughts), fewer external distractions, and more goal-oriented content and imagery. Importantly, resting state functional connectivity analyses revealed group differences in default and frontoparietal control networks, which have been implicated in off-task thought in young adults. Overall, these findings shed light on the content, mental health correlates, and neural underpinnings of off-task thinking in young and older adults.

**Disclosures: J.R. Andrews-Hanna:** None. **C.K. Gardiner:** None. **M.T. Banich:** None. **A.D. Bryan:** None.

**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

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**Program#/Poster#:** 527.16/VV41

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant R01AG047972-01A1

**Title:** Increasing age differences in neural-vascular coupling with increasing task demand revealed by calibrated fMRI

**Authors: M. P. TURNER**[1], D. K. SIVAKOLUNDU[2], B. P. THOMAS[4], K. L. WEST[3], Y. ZHAO[3], H. LU[6], *B. P. RYPMA[3,5]
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**Abstract:** Extant theories of neurocognitive aging are largely based on age differences in blood-oxygen-level-dependent signal (BOLD) as measured with functional magnetic resonance imaging (fMRI). Straightforward interpretation of age-related changes in BOLD as an index of age-related changes in neural activity depends upon the assumption that BOLD increases monotonically with increasing task demand. We sought to test this assumption across age groups by disentangling two physiologic factors underlying BOLD: (1) Cerebral blood flow (CBF), known to change with age, quantifies oxygen delivery to neurons undergoing changes in (2) cerebral metabolic rate of oxygen ($CMRO_2$). Taken together, these two factors reflect the integrity of the neural-vascular coupling mechanism. Sixteen healthy younger (mean age = 23.6, SD = 3.4, 10 F) and eighteen healthy older (mean age = 58.9, SD = 4.6, 11 F) right-handed adults performed block-designed visual and motor tasks while undergoing calibrated fMRI scanning. Participants were screened for any potential cardiologic, respiratory, pulmonary, or vascular conditions. During the visual task, participants responded via bilateral button-press whenever a fixation cross at center-screen changed in luminance; during stimulation blocks, flickering checkerboards were presented at varying frequencies (2 Hz, 4 Hz, and 8 Hz). During the motor task, participants pressed buttons bilaterally in rhythm with an auditory cue (1 Hz, 2 Hz, and 3 Hz). To estimate maximum possible BOLD, participants completed a hypercapnia challenge, in which they breathed room air for 4 minutes and then a gas containing 5% CO2 21% O2, and 74% N2 for 6 minutes while being scanned at rest. During all functional scans, BOLD and CBF were collected in separate echoes using a novel pCASL-based sequence (parameters TE1/TE2=11/30 ms, TR = 4 s, 22 6-mm axial slices, no gap, in-plane=3.4×3.4 $mm^2$). In visual cortex, during visual stimulation, younger participants exhibited monotonic increases in both BOLD and CBF with increasing task demand. Older participants exhibited decreases in BOLD with increasing task demand. CBF for older participants plateaued at higher task demand. Similar results were observed in motor cortex during motor task performance. Non-equivalence of BOLD-signal monotonicity with task demand between age groups does not support the assumption that BOLD is proportional to local neural activity in older adults as it is in younger adults. Apparent BOLD decreases with increasing task demand, irrespective of cognitive demand, in older participants might be a result of inability to sustain neural-vascular coupling in the face of increasing task demand.

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**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 527.17/VV42

**Topic:** H.02. Human Cognition and Behavior

**Support:** Marie Skłodowska-Curie Actions (MSCA)

**Title:** Modulation of alpha oscillations in humans during allocation of internal resources in relation to sub-regions of the striatum: Effects of aging

**Authors:** ***S. AURTENETXE**[1], E. VAN BIJNEN[1], R. KESSELS[2], A. NOBRE[3], O. JENSEN[4]
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**Abstract:** Spatial attention to external information modulates neural oscillatory activity of the human brain. Processing relevant information is believed to be supported by oscillations at higher frequencies (gamma range, >30 Hz), whereas inhibition of task-irrelevant information is believed to be supported by oscillations at low frequencies (alpha range, 8-13 Hz). In a similar manner, directing attention to internal representations (as revealed in retro-cue paradigms), has been shown to be supported by analogous mechanisms. It is well established that attention and working memory (WM) functions decline with age. This decline is possibly explained by altered top-down control or compensatory mechanism involving the fronto-striatal network. The aim of this project is to identify striatal regions relating to the reduced ability to modulate posterior oscillations in the elderly. In the current study, 30 young and 30 older participants (18-30 and 58-70 years old respectively and matched on education) performed a retro-cue task while their respective neural activity was recorded with magnetoencephalography (MEG). In addition, each participant underwent structural brain image scanning and neuropsychological assessment. Centrally presented retro-cues induced lateralized patterns of alpha power in occipital sensors depending on whether the relevant stimuli were located left or right during the encoding. This lateralization was reduced in the older adults. From the structural brain scans we identified the volume of the subregions of the basal ganglia using FSL-FIRST. We correlated the hemispheric asymmetry in these subregions with the ability to modulate alpha in response to the retro-cue. Importantly, those elderly who showed a left hemispheric bias in their ability to modulate alpha power also showed reduced volume of the globus pallidus (GP) in the right hemisphere.Our findings demonstrate a role for alpha oscillations when directing attention towards internal representations. The ability to modulate alpha oscillations when orienting to internal

representation is diminished in the elderly. Importantly, the current preliminary results point that structural changes in the GP in the elderly are associated with a reduced ability to modulate alpha oscillations. In future work we aim to elucidate if these structural changes are compensatory or directly involved in the top-down control.

**Disclosures: S. Aurtenetxe:** None. **E. van Bijnen:** None. **R. Kessels:** None. **A. Nobre:** None. **O. Jensen:** None.

**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

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**Program#/Poster#:** 527.18/VV43

**Topic:** H.02. Human Cognition and Behavior

**Support:** TL1TR001428

NIH Award AG044862

**Title:** Anatomical substrates of cognitive fatigue and fatigability in aging

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**Abstract:** Cognitive fatigue is a disorder of extreme unrelenting mental exhaustion. It can result in severe disability, diminished quality of life, and even increased mortality. Cognitive fatigue affects an estimated 38% of the healthy aged population. However, this number does not include the many individuals that suffer from fatigue as a comorbidity of age-related diseases. The state level perception of cognitive fatigue is widely assessed by the Fatigue Severity Scale (FSS). There is, however, no effective instrument to measure an individual's susceptibility to develop fatigue for a given workload, referred to as fatigability. In addition, the neural substrate of cognitive fatigue and fatigability remains unknown. To address these gaps in knowledge, we recruited 37 older fatigued adults to undergo cognitive behavioral testing and MRI scanning. To test performance fatigability, we conducted a 2.5 hour cognitively demanding task, the Stroop Task. Behavioral measures (e.g., reaction times) were collected simultaneously with physiological measures (pupillometry). Further, subjective assessments were collected as participants rated their fatigue level every 20 minutes throughout the task. On a separate visit, participants will undergo structural and diffusion imaging to evaluate gray matter and white matter integrity. Through the analysis of fatigue and fatigability measures, we intend to show that an objective performance fatigability index can derived from behavioral performance. This

index will be validated via simultaneous subjective and physiological assessments. A priori regions of interest, the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC), will be analyzed via structural and diffusion MRI scans. These regions are both vulnerable to aging and have crucial roles in cognitive control functions that are related to fatigue and fatigability. Specifically, the DLPFC is responsible for behavioral action and the ACC is related to perception. Therefore, we will test the hypothesis that perceived fatigue is related to atrophy in the ACC and that performance fatigability is related to network disruption within DLPFC.

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**Poster**

**527. Cognitive Aging**

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**Support:** NIH/NIA K01AG050707

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The Center for Cognitive Aging and Memory at the University of Florida

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**Title:** Tissue correction strategies impact GABA-edited MRS findings

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**Abstract:** Tissue composition impacts metabolite quantification. The goal of applying tissue correction is to decrease the dependency of metabolite concentrations on the underlying voxel tissue composition. Different tissue correction strategies have different underlying assumptions

and account for different aspects of the voxel tissue fraction. The most common tissue correction is the CSF-correction, which aims to account for the CSF fraction in the voxel in which it is assumed there are no metabolites. More recently, the α-correction was introduced to account for the different concentration of GABA in grey matter compared to white matter. In this paper, using a healthy aging cohort, we show that the selection of tissue correction strategy can alter the interpretation. In a frontal voxel, we show an age-related decline in GABA when no tissue correction ($R2= 0.25$, $p < 0.001$) or the CSF-correction is applied ($R2= 0.08$, $p < 0.01$). However, when applying the α-correction, there is no relationship between age and GABA ($R2= 0.02$, $p = 0.15$). This indicates that the selection of tissue correction can significantly impact the interpretation of MRS results. Furthermore, this data shows that in healthy aging, while there is normal atrophy, the GABA concentration in the remaining tissue is not decreasing.

**Disclosures:** **E.C. Porges:** None. **A.J. Woods:** None. **D.G. Lamb:** None. **J.B. Williamson:** None. **R.A. Cohen:** None. **R.A.E. Edden:** None. **A.D. Harris:** None.

**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 527.20/VV45

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant R01AG050523

**Title:** Neural distinctiveness and GABA concentrations in the aging ventral visual cortex

**Authors: *J. D. CHAMBERLAIN**[1], H. GAGNON[2], P. S. LALWANI[3], K. E. CASSADY[4], M. SIMMONITE[3], B. FOERSTER[2], M. PETROU[2], R. D. SEIDLER[2], S. F. TAYLOR[5], D. WEISSMAN[2], T. A. POLK[6]
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**Abstract:** Previous functional magnetic resonance imaging (fMRI) work in humans has demonstrated that neural activity associated with different visual stimulus categories (e.g., faces and houses) becomes less distinguishable with age. Furthermore, this decline in neural distinctiveness predicts age-related declines in fluid processing ability. One hypothesis about why neural distinctiveness declines with age is based on changes in gamma-aminobutyric acid (GABA) concentrations. Studies in nonhuman primates have found that GABA levels decline with age, and increasing GABA levels experimentally increases the selectivity of receptive fields in visual neurons of older macaques. In this study, we investigated whether individual differences in GABA levels in ventral visual cortex predict individual differences in neural

distinctiveness in human beings. Older and younger adults completed a six-minute fMRI task in which they passively viewed greyscale images of faces and houses, and responded to occasional target images. Multi-voxel pattern analysis (MVPA) of activation patterns in the bilateral fusiform gyrus and parahippocampal gyrus was used to estimate the neural distinctiveness of face and house representations. Magnetic resonance spectroscopy (MRS) was used to estimate GABA concentrations in ventral visual areas that were activated by the fMRI tasks. Multiple regression analysis was conducted to examine changes in neural distinctiveness and GABA concentrations with age, as well as the relationship between neural distinctiveness and GABA level. While data collection is ongoing, neural distinctiveness and GABA concentrations declined with increasing age in 9 younger and 9 older adults. Additionally, GABA concentrations in right ventral visual cortex significantly predicted neural distinctiveness, and a backward elimination stepwise regression demonstrated that GABA concentration was a better predictor of distinctiveness than age group. These findings indicate a relationship between neural distinctiveness and GABA concentrations in the ventral visual cortex, and support the hypothesis that age-related reductions in GABA concentrations contribute to age-related declines in neural distinctiveness.

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**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 527.21/VV46

**Topic:** H.02. Human Cognition and Behavior

**Title:** Facilitating scalable cognitive science research through the human cognition project

**Authors: *E. CORDELL**, K. KERLAN, N. NG, B. SCHAFER
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**Abstract:** Advancements in our understanding of human cognition have been tempered by the methodological constraints that characterize the domain of cognitive science research. At present day, investigators tackle individual research hypotheses by conducting discrete, small-scale studies of cognition with insufficient sample sizes, low power, and incomparable task designs. The result is an unsystematic and fragmented body of cognitive research literature, comprised of studies that are time consuming, costly, and difficult to replicate.
The Human Cognition Project (HCP) is an online platform created to facilitate large-scale, collaborative research studies, led by independent academicians and clinicians. The goal of the HCP is to advance our understanding of human cognition by supporting research collaborators

world-wide in their pursuit of efficiently conducting well-powered research initiatives. Inspired by Lumosity's web-based cognitive training platform, qualified research collaborators are granted fully-customized access to a suite of online cognitive training tasks, neuropsychological assessments, surveys, tracking metrics, and other research tools. Additionally, research collaborators have access to the largest database of human cognitive performance, with data from over 80 million individuals to date.
The HCP is guided by the hypothesis that bringing together a broad network of academic scientists and clinicians will accelerate our understanding of normal and disordered cognitive performance across the lifespan, thereby advancing the field of human cognition. Since the project formally began in 2011, HCP has resulted in twelve peer-reviewed publications. Here we will present an overview of the HCP platform as well as several primary findings from published studies that have resulted from the project.

**Disclosures:** **E. Cordell:** A. Employment/Salary (full or part-time):; Lumos Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lumos Labs. **K. Kerlan:** None. **N. Ng:** A. Employment/Salary (full or part-time):; Lumos Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lumos Labs. **B. Schafer:** A. Employment/Salary (full or part-time):; Lumos Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lumos Labs.

**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 527.22/VV47

**Topic:** H.02. Human Cognition and Behavior

**Support:** Anita Kunin Professorship for Women's Healthy Brain Aging (LJ)

**Title:** Effects of dietary habits and genotype on neural network properties

**Authors: *S. DOLAN**[1], L. JAMES[2], A. C. LEUTHOLD[3], A. P. GEORGOPOULOS[4]
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**Abstract:** Genetics and lifestyle play important roles in healthy aging. For instance, apolipoprotein E (apoE) is widely known to be associated with age-related cognitive changes, and dietary habits are well known to be linked to overall health. Here we evaluated brain health as it relates to apoE genotype and dietary habits in cognitively healthy (MoCA $\geq$ 26) participants.

Participants record food and beverage intake for three days, two weekdays and one weekend day. The items are then entered into Nutritionist Pro Version 6 to quantify over 100 macro- and micro-nutrients, including amino acids, trace minerals, and lipids. Participants also provide a blood sample for apoE genotyping and undergo a MEG scan. We analyzed properties of the neural network, including the flexibility and variability of interactions between MEG sensor pairs as it relates to genotype and dietary habits. Results demonstrated that network properties varied by genotype and were moderated to some extent by dietary habits. These findings highlight the importance of lifestyle factors in moderating brain health, particularly in those with at-risk genotypes.

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**Poster**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** MOP-FDN-148418

**Title:** Changes in cognitive pupil responses across the lifespan

**Authors: *J. HUANG**, M. L. SMORENBURG, B. C. COE, C.-A. WANG, D. P. MUNOZ
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**Abstract:** Change in cognitive functions occurs as a result of natural development and aging, with maturation processes in childhood and deterioration in old age. Pupil size is an easy-to-measure index that is increasingly used to assess cognitive function. Neurophysiological experiments have shown that pupil size is modulated by converging inputs from both bottom-up sensory and top-down cognitive signals. In order to use pupil responses as potential biomarker of diseases, we must first understand changes in pupil response across the lifespan. Here, we examined pupil dynamics in different ages across the healthy lifespan, and hypothesized that modulation of pupil response by top-down signals should change with age, due to delayed frontal maturation in children and cognitive decline in the aging population. Pupil size was recorded in healthy subjects (age 5-85) while performing the interleaved pro- and anti-saccade task. Subjects were instructed via the colour of a fixation cue to generate either an automatic eye movement toward a peripheral stimulus (pro-saccade) or a voluntary eye movement in the opposite direction (anti-saccade). The pupil response consisted of an initial constriction shortly after the presentation of a fixation cue, followed by pupil dilation. Analysis showed age-related effects in each component of pupil response: baseline pupil size decreased with age, and the latency of

peak constriction was longer with increased age. Pupil dilation velocity also decreased with age, and the modulation of pupil dilation by saccade preparation showed age-related decrease that may link to changes of different brain regions in development and aging. The results demonstrated changes in pupil dynamics linked with development and aging, providing the baseline with which abnormal pupil responses due to neurological deficits can be studied.

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**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

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**Topic:** H.02. Human Cognition and Behavior

**Support:** Portuguese Foundation for Science and Technology (FCT, Portugal SFRH/BD/90078/2012)

**Title:** Bridging gaps: Validating use of rapid testing through technology for cognitive assessment in aging

**Authors: *T. C. CASTANHO**[1,2,3], L. AMORIM[1,2,3], P. MOREIRA[1,2,3], J. A. PALHA[1,2,3], N. SOUSA[1,2,3], N. C. SANTOS[1,2,3]
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**Abstract:** To provide feasible and rapid assessment tools to assist in cognitive diagnosis in research and clinical practice, as well as to establish thresholds for cognitive impairment, adapted to the Portuguese context, the applicability of rapid cognitive screening (TICSM-PT) through technology was explored. Results indicated that the TICSM-PT presents associations not only with global cognitive measures, but also with a number of cognitive and psychological instruments performed in-person. Moreover, it demonstrated to be a practical tool for rapid cognitive assessment, and a valid method of screening cognition by telephone. Using a different technological approach, but the same instrument, it was further demonstrated that is possible to carry out accurate and reliable cognitive assessments using videoconference with individuals from different settings with a diagnostic cognitive spectrum from normal to dementia. Findings indicate that the videoconference administration method yields comparable results to the traditional face-to-face administration. The participants also demonstrated to be "at ease" throughout the videoconference test administration and that there was no significant difference in approaches between locales. The findings of this study indicate that cognitive test assessment via

videoconferencing is a tool for consideration by the health professionals to reliably follow-up their patients who live in different settings. In order to make the study more robust and disseminate the practice of telemedicine, more evaluations are ongoing. From a clinical and research point of view, the implementation of home-based technologies for cognitive test administration both enables a cut with the burden of travelling to the hospital and, also, a close patient follow-up of individuals living anywhere.

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**Poster**

**527. Cognitive Aging**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** CIHR operating grant (LS), MOP#125915

**Title:** A 16-week visuomotor exercise program improves overall cognition and functional abilities in older adults with cognitive impairment

**Authors: *C. DE BOER**[1], A. ROGOJIN[2], B.-R. BALTARETU[3], H. ECHLIN[4], L. E. SERGIO[5]
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**Abstract:** To efficiently interact with the environment, our brain continuously has to make accurate visuomotor transformations. This process requires well-functioning large cortical-subcortical neural networks, particularly during cognitively challenging tasks, e.g. when vision and motor action are dissociated. In recent years, evidence has emerged that large neural networks, such as those involved in visuomotor transformations, are particularly vulnerable to the early-stage neurodegenerative effects of dementia. This implies that preservation of neural network integrity and functioning is an important target for early-stage intervention strategies. Here, we present behavioural data on the effects of a tablet-based visuomotor exercise program in older adults with various degrees of cognitive impairment. The overall goal of this study is to assess whether such exercises may maintain neural network integrity and its functional counterparts in this population. A 16-week visuomotor training program (1 session/week, 30 min/session) was completed by 39 elderly (13 controls, 8 sub-average cognition, 8 mild cognitive deficits, 10 severe cognitive deficits). Visuomotor exercises involved making goal-directed finger sliding movements on a tablet by playing the videogame Fruit Ninja®. Several variations designed to integrate cognition and motor action were implemented, including visual

plane dissociation and proprioceptive feedback reversal. Pre-and post training, all participants completed a test battery to measure their level of cognition, functional independence in daily life (caregiver rated), and visuomotor functioning. All subgroups significantly improved their game scores at all difficulty levels after training. Older adults that completed the program showed mildly improved cognitive scores (Dementia Rating Scale: mean increase 3.3 points, Montreal Cognitive Assessment: mean increase 1.4 points). Functionally, those elderly with cognitive impairment showed signs of improved visuomotor functioning, displaying faster response times, faster movement times, and better movement accuracy ($p<0.05$). This coincided with a stabilization of caregiver reported scores of functional independence. These results provide behavioral evidence that (1) improving visuomotor functioning in elderly with cognitive impairment can transfer to improved cognition and functional skills, and (2) neural networks in these elderly may still possess a degree of neuroplasticity. We are currently testing this latter idea by assessing possible exercise related changes in neural network integrity through MRI imaging.

**Disclosures: C. De Boer:** None. **A. Rogojin:** None. **B. Baltaretu:** None. **H. Echlin:** None. **L.E. Sergio:** None.

**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 527.26/VV51

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIA/NIH Grant U01 AG016976

**Title:** Associations between cardiovascular risk factors and cognition in aging Hispanics compared to Non-Hispanic Whites

**Authors: *A. STICKEL**[1], L. RYAN[2]
[1]Psychology, [2]Evelyn F. McKnight Brain Inst., Univ. of Arizona, Tucson, AZ

**Abstract:** The presence of one or more cardiovascular risk factors is associated with poorer cognitive abilities (e.g., processing speed, executive functions). In cohorts of Hispanics and non-Hispanic Whites with cardiovascular risk factors, Hispanics tended to live longer than Whites. This finding, known as the Hispanic paradox, is robust. However, it is unclear whether the Hispanic paradox confers protection on cognitive processes. The present study compared relationships between cardiovascular risk and cognition in late-middle age and older Hispanics (n = 67) and non-Hispanic Whites (n = 67) selected from the National Alzheimer's Coordinating Center (NACC)* database. Participants included healthy controls (n = 90) and individuals with mild cognitive impairment (n = 44). Hispanics and non-Hispanic Whites were matched on age (50-94 years, mean age = 72 years), gender, cognitive status (i.e., cognitively healthy versus

MCI), hypertension, and apolipoprotein e4 status. Hispanics had higher body mass index (BMI) and fewer years of education, on average, than Non-Hispanic Whites. A neuropsychological battery of tests was administered to all participants. Tests of interest were Forward Digit Span, Backward Digit Span, Logical Memory Long Delay Recall, phonemic fluency (F-A-S), semantic fluency (Animals), and the Boston Naming Test. In SPSS, the general linear models tested if cardiovascular risk factors influenced cognition differentially for Hispanics compared to Non-Hispanic Whites, controlling for age and education. Associations between cardiovascular risk and cognition differed between Hispanics and Non-Hispanic Whites. These risk factors predicted poorer cognition in Hispanic individuals but not Non-Hispanic Whites, particularly on measures of executive functions, including working memory (Backward Digit Span) as well as semantic fluency (Animals). No main effects of hypertension or BMI were detected. Taken together, cardiovascular health influenced cognition among Hispanics to a greater degree than non-Hispanic Whites. This finding is contrary to the notion of a Hispanic Paradox-like protection on cognitive processes.
*The NACC database is funded by NIA/NIH Grant U01 AG016976.

**Disclosures:** **A. Stickel:** None. **L. Ryan:** None.

**Poster**

**527. Cognitive Aging**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 527.27/VV52

**Topic:** G.07. Other Psychiatric Disorders

**Title:** SUVN-502 (pure 5-$HT_6$ antagonist): A promising therapeutic potential for menopause associated dementia

**Authors: V. GRANDHI**, J. TADIPARTHI, N. GANUGA, R. MEDAPATI, *P. JAYARAJAN, R. NIROGI
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**Abstract:** Human life expectancy has increased from 75 to 83 years in developed countries over the last century. However, the age at which women encounters major hormonal change, i.e. menopause transition has essentially remained constant at around 50 years. Women spend over one-third of their life time in post menopausal state with chronic decline in circulating hormones, making women prone to degenerative changes and disability. Evidence shows that post-menopausal women are highly susceptible to dementia and Alzheimer's Disease (AD) which has negative impact on quality of life. Although donepezil or hormonal therapy (HT) were tried clinically, the outcome was not satisfactory. Moreover, there could be increased risk of coronary heart disease, pulmonary embolism, ovarian and breast cancers with HT. No effective and alternative intervention is available or approved till date for cognitive deficits associated with

menopause. SUVN-502, a pure 5-$HT_6$ receptor antagonist was evaluated for its potential to alleviate menopause related dementia in a neuro-cognitive animal model of surgical menopause. Bilateral ovariectomy was conducted in female Wistar rats to induce surgical menopause state. Following the recovery period (4-weeks), animals were evaluated for episodic memory, i.e. novel object recognition task (NORT). SUVN-502 was evaluated in two different experiments based on either acute (2-days) or sub-acute (17-days) treatment at 1, 3 and 10 mg/kg, *p.o.* Donepezil (1 mg/kg, *i.p.*) group was included in both models. Object exploration time and discriminative index were assessed. Acute treatment with SUVN-502 dose dependently reversed surgical menopause-induced object memory deficits. A significant improvement in discriminative index was observed in SUVN-502 10 mg/kg, *p.o.* treatment group when compared to vehicle and donepezil treated groups. Sub-acute treatment (17-days) with SUVN-502 further enhanced object recognition memory dose dependently. Vehicle treated rats did not discriminate between the objects, whereas rats treated with SUVN-502 spent significantly more time exploring novel object as compared to familiar one. Significant improvement in discriminative index was observed for groups treated with SUVN-502 at 3 and 10 mg/kg, *p.o.* when compared to vehicle or donepezil groups. Donepezil did not reverse deficits in both the experiments, which is in accord with the clinical outcome. These results indicate that SUVN-502 could be a promising therapeutic strategy in post-menopause associated dementia and AD.

**Disclosures:** **V. Grandhi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **J. Tadiparthi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Ganuga:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Medapati:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.01/VV53

**Topic:** I.04. Physiological Methods

**Support:** Brain initiative UO1NS090498

**Title:** An all-optical system for rapid and deep interrogation of behaviorally relevant activity patterns

**Authors: *G. M. LERMAN**[1], J. V. GILL[2], D. RINBERG[3], S. SHOHAM[4,3]
[1]Neurosci., New York Univ. Sch. of Med., New York, NY; [2]Ctr. for Neural Sci., [3]New York Univ., New York, NY; [4]Technion, Haifa, Israel

**Abstract:** Holographic optogenetics is an emerging tool for distributed control of spatiotemporal neuronal activity. Establishing causality between specific sequences of neuronal activity and behavior requires manipulating this code at the level of individual neurons while recording neural responses and behavioral readout. However, traditional methods of optogenetic perturbation lack the ability to emulate natural patterns of neural activity, or to rapidly alter the activity of specific neurons deep in the brain. To address the goal of producing behaviorally relevant sequences of neural activity, we have developed an all-optical, rapid two-photon optogenetic stimulation and imaging system with cellular resolution and 5 ms temporal precision. Using an amplified laser with high peak pulse power, together with wavefront shaping methods using a fast spatial light modulator (3 ms switching time), we were able to stimulate dozens of neurons deep in the olfactory bulb (>350 μm) at a high rate (>100 Hz) with cellular resolution. We optimized the system parameters to enable efficient excitation with a low power budget, to enable the simultaneous stimulation of many cells (~60). We then demonstrated stimulation of mitral and tufted cells, the projection neurons of the olfactory bulb, at a high rate, generating artificial odor-evoked responses. We will present the system characteristics and discuss its potential applications for manipulating and reading neuronal activity on a behaviorally relevant spatiotemporal scale to dissect the activity codes that guide behavior across different modalities.

**Disclosures: G.M. Lerman:** None. **J.V. Gill:** None. **D. Rinberg:** None. **S. Shoham:** None.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.02/VV54

**Topic:** H.01. Animal Cognition and Behavior

**Support:** RIA's Howard T. Blane Director's Award for Development of Innovative Research in the Addictions (BDAA)

**Title:** Effects of wireless optogenetic stimulation of medial prefrontal pyramidal neurons on within-session habituation of locomotor activity in freely moving rats

**Authors: *K. ISHIWARI**, A. M. GEORGE, C. D. MARTIN, R. Y. SHEN, S. HAJ-DAHMANE, J. B. RICHARDS
Res. Inst. on Addictions, Univ. at Buffalo, Buffalo, NY

**Abstract:** In rodents, exploratory locomotor activity in a novel environment diminishes over time and with repeated exposures and displays behavioral characteristics of habituation, such as spontaneous recovery and dishabituation. However, little is known about the brain circuitry involved in locomotor habituation. The present study examined effects of optical stimulation of

pyramidal neurons in the medial prefrontal cortex (mPFC) on intra-session habituation of locomotor activity in freely moving rats using a wireless optogenetic system. Adult male Sprague Dawley rats were randomly assigned to two groups. One group was unilaterally injected with an adeno-associated viral vector encoding channelrhodopsin-2 (ChR2) under the control of CaMKIIα promoter (AAV9.CaMKIIα.hChR2(H134R)-eYFP) into the mPFC, while a second group received a control vector encoding only a fluorescent protein (GFP). Both groups were implanted unilaterally with a semi-rigid shank (8 mm in length, 0.55 mm in width, and 0.035 mm in thickness) with an LED (0.32 mm × 0.24 mm × 0.14 mm, $\lambda = 465$ nm) at the site of virus injection. Four weeks after virus injection, rats were tested for locomotor activity in a dark plastic test chamber (42.5 cm × 22.5 cm × 19.5 cm) equipped with an infrared motion-sensor system and located in a sound- and light-attenuating enclosure in two 30-min sessions. Rats were tested twice to ensure the reproducibility of the results. The two sessions were conducted in different chambers and separated by a minimum of four days to allow for spontaneous recovery and minimize inter-session habituation. In both sessions, rats were allowed to explore and habituate for 18 min, and then blue light pulse trains (10 ms, 20 Hz, 13 mW, 15 s on and 15 s off for 6 cycles) were delivered wirelessly for 3 min. The GFP group underwent the same light stimulation procedure as the ChR2 group, providing a control for the effects of light alone. The results showed significant increases in activity and distance traveled in the 3-min period in which stimulation was delivered in the ChR2 group, while no such increases were observed in the control group. Thus, with the stimulation parameters used, optical stimulation of mPFC pyramidal neurons had dishabituating effects on locomotor activity. Future research needs to further elucidate the circuitry involved in locomotor habituation. The present results demonstrate the feasibility of using a wireless optogenetic system in freely moving rats.

**Disclosures: K. Ishiwari:** None. **A.M. George:** None. **C.D. Martin:** None. **R.Y. Shen:** None. **S. Haj-Dahmane:** None. **J.B. Richards:** None.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.03/VV55

**Topic:** I.04. Physiological Methods

**Title:** Enhanced light delivery to multiwell microplates for high throughput optical control of activity and cellular processes

**Authors: I. P. CLEMENTS**, D. C. MILLARD, M. CLEMENTS, A. M. NICOLINI, S. A. CHVATAL, *H. B. HAYES, J. D. ROSS
Axion Biosystems, Atlanta, GA

**Abstract:** Optical stimulation techniques including optogenetics methodologies enable control over cultured cells, tissues, and small organisms. Patterns of neural activity, gene expression, protein localization, and iPSC-derived maturation or network development, can all be influenced with specificity and precision via non-invasive optical stimulation. Here, we describe a system for high-throughput light delivery to multiwell microplates for a wide range of applications in neuroscience. Light of up to four wavelengths is delivered to each well of a multiwell (*e.g.* 24, 48, 96) microplate with flexible and precise control over intensity and timing for each wavelength and well. Optical specializations enable high maximum irradiance, even light delivery across the culture substrate, and elimination of light bleed-through between wells. These capabilities are achieved with a top-side light delivery format, leaving the bottom of the microplate open for optional simultaneous imaging, electrophysiology, temperature control, or other interfacing modalities. Provisions for environmental control enable long-term light delivery experiments, such as optical modulation of activity, gene expression, or intracellular pathways during development/maturation. Proof-of-concept applications are given to demonstrate the utility of this system to enable scalable, high throughput control of critical biological parameters, with the additional capability to pair with complementary technologies such as electrophysiology or imaging.

**Disclosures: I.P. Clements:** A. Employment/Salary (full or part-time):; Axion BioSystems. **D.C. Millard:** A. Employment/Salary (full or part-time):; Axion BioSystems. **M. Clements:** A. Employment/Salary (full or part-time):; Axion BioSystems. **A.M. Nicolini:** A. Employment/Salary (full or part-time):; Axion BioSystems. **S.A. Chvatal:** A. Employment/Salary (full or part-time):; Axion BioSystems. **H.B. Hayes:** A. Employment/Salary (full or part-time):; Axion BioSystems. **J.D. Ross:** A. Employment/Salary (full or part-time):; Axion BioSystems.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.04/VV56

**Topic:** I.04. Physiological Methods

**Support:** Darpa Contract W911NF-15-C-0069

**Title:** Implantable neural recording and stimulation capsules for *In vivo* electrophysiology

**Authors: *J. C. MORIZIO**, V. GO, D. PEREZ
Triangle Biosystems, Inc, Durham, NC

**Abstract:** Over the last decade, wireless technology advancements for neural recording and stimulation continue to improve with respect to data rates, power consumption, weight and size

thus inspiring new experiments for in vivo electrophysiology research on freely moving rodents. In this presentation, we present the latest technology enhancements to a neural recording system using telemetric implantable capsules that can record from 5 to 128 channels of EEG, EMG, ECG, and single units or spikes signals simultaneously in real time. In addition, we present an implantable neural stimulation system which includes full duplex digital transceiver capsules that can stimulate 2 channel or 16 channel constant current bipolar pulses or 2 channel optogenetic stimulation. Key design challenges and trade-offs of these implantable wireless technologies will be explained. Sub-system components and accessories will also be described that include electrodes and neural interfaces, as well as low noise integrated CMOS electronics, RF transceiver circuitry, 90-day packaging, coating processes and inductive powering technologies. Test data from rat, pigs and NHP with electrical specifications for each of the implantable technologies will also be presented. DAQ analysis software used for neural recording and stimulation for pattern definition and triggering will conclude the presentation.

**Disclosures:** **J.C. Morizio:** None. **V. go:** None. **D. Perez:** None.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.05/VV57

**Topic:** I.04. Physiological Methods

**Support:** NIH/NINDS R00NS078118

NIH/NINDS R01NS096369

Gladstone Institutes

Kavli Institute for Fundamental Neuroscience

DoD (EP150038)

NSF (# 1608236)

NSF #1650113

**Title:** Distinct thalamic reticular cell types differentially modulate normal and pathological cortical rhythms

**Authors: *A. CLEMEMTE**[1], S. L. MAKINSON[2], B. HIGASHIKUBO[3], S. BROVARNEY[3], F. S. CHO[4], A. URRY[3], S. HOLDEN[5], M. WIMER[3], L. E. FENNO[6], C. DAVID[7], L. ACSADY[8], K. DEISSEROTH[9], J. PAZ[10]
[1]GIND, Univ. of California, San Francisco, CA; [2]Neurolog. Dis., [3]Gladstone Inst., San Francisco, CA; [4]Neurosci., [5]UCSF, San Francisco, CA; [6]Neurosci., Stanford Univ., Stanford, CA; [7]Lab. of Thalamus, Budapest, Hungary; [8]Inst. Exp. Med. Hung Acad Sci., Budapest, Hungary; [9]Bioengin & Psych, Stanford Univ. Dept. of Psychology, Stanford, CA; [10]Neurol., Gladstone Inst. of Neurolog. Dis., San Francisco, CA

**Abstract:** Integrative brain functions depend on widely distributed, rhythmically coordinated computations. Through its long-ranging connections with cortex and most senses, the thalamus orchestrates the flow of cognitive and sensory information. Essential in this process, the nucleus reticularis thalami (nRT) gates different information streams through its extensive inhibition onto other thalamic nuclei; however, we lack an understanding of how different inhibitory neuron subpopulations in nRT function as gatekeepers. We dissociated the connectivity, physiology, and circuit functions of neurons within rodent nRT, based on parvalbumin (PV) and somatostatin (SOM) expression, and validated the existence of such populations in human nRT. We found that PV but not SOM cells are rhythmogenic, and that PV and SOM neurons are connected to and modulate distinct thalamocortical circuits. Notably, PV but not SOM neurons modulate somatosensory behavior and disrupt seizures. These results provide a conceptual framework for how nRT may gate incoming information to modulate brainwide rhythms

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**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.06/VV58

**Topic:** I.04. Physiological Methods

**Support:** NSF STC award CCF - 123 1216

Center for Brains, Minds and Machines (CBMM)

1F32MH107086-01

**Title:** An open-source PCIe based electrophysiology system for high data rate, low-latency closed-loop experiments

**Authors: *J. P. NEWMAN**[1], J. ZHANG[2], J. VOIGTS[3], A. CUEVAS LOPEZ[5], M. A. WILSON[4]
[1]Dept. of Brain and Cognitive Sci., [2]BCS, [4]Picower Inst. Learn/Memory, [3]MIT, Cambridge, MA; [5]Dept. de Ingeniería Electrónica, Univ. Politècnica De València, Valencia, Spain

**Abstract:** Testing increasingly specific hypotheses about the necessity and sufficiency of the neural codes for behaviors requires closed-loop experiments that can execute complex control algorithms on fast timescales. While many existing solutions can cope with high data rates or low latencies, it is still technically challenging to develop and perform such experiments, and few standards exist that ensure interoperability of hardware and software components and that would allow researchers to share methods and replicate experiments.
We have developed an electrophysiology system that implements a full bi-directional data pipeline between headstages and software at sufficiently low latencies to implement closed-loop control algorithms entirely in software on a commodity PC. The system has two main hardware components. First is a 256-channel headstage (using neural amplifier chips from Intan Technologies) for use with behaving rats, with integrated FPGA, high-bandwidth data serializer, 9-axis IMU, and 32-channel LED driver. Second is an galvanically-isolated PC-housed acquisition board containing headstage deserialization circuitry, multi logical-level GPIO, and FMC interfacing circuitry. PCIe communication is provided by a commodity, and easily upgradable, FPGA development board (Xilinx KC705). Communication and power between the headstage and acquisition board board is provided by a single coaxial tether, which is easily commutated.
The acquisition system makes full use of the high bandwidth and low latency of the PCIe bus and is capable of recording and reacting to over 1000 channels of electrophysiology in significantly under 1ms round-trip latency. The system is based on a commodity FPGA evaluation board and industry standard FMC interconnects and can easily be extended to use other data sources. Similarly, the system can be integrated into new software easily through a common API. This library facilitates parallelized acquisition and processing of data streams in (potentially multiple) userland applications. Using this API, we have created a plugin for the Open Ephys GUI. All hardware and software designs are publically available along with detailed documentations concerning hardware acquisition, system setup and usage.

**Disclosures:** **J.P. Newman:** None. **J. Zhang:** None. **J. Voigts:** None. **A. Cuevas Lopez:** None. **M.A. Wilson:** None.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.07/VV59

**Topic:** I.04. Physiological Methods

**Support:** ANR Holohub

ERC Consolidator Neuropionners

**Title:** Dissecting the functional structure of CA1 assemblies with light

**Authors: *T. TRESSARD**[1], E. RONZITTI[2], A. MALVACHE[1], E. PAPAGIAKOUMOU[2], V. EMILIANI[2], R. COSSART[1]
[1]INMED, INSERM U-901, Marseille, France; [2]Neurophotonics Lab., Paris, France

**Abstract:** The CA1 region of the hippocampus has been recently shown to be functionally organized in neural assemblies which are successively recruited during experience and independently recalled during replay events (Malvache Science 2016). Such functional topology could either be shaped by common inputs from upstream regions or arise from local inhibitory circuits. In the latter case, CA1 assemblies would be shaped by the local activity of pyramidal neurons. In order to test this hypothesis, we use an all-optical approach in the hippocampus taking advantage of the fast opsin Chronos (Klapoetke Nat Methods 2014, Ronzitti bioRxiv 2016). First, we have optimized the expression of Chronos-Td-Tomato and GCamp6s in the dorsal hippocampus of mice using multi-site viral infections for a large spreading and an efficient co-expression. Quantification was made using histology to confirm the compatibility for large scale in vivo two photon imaging. We compared the level of neuronal activity reported by calcium imaging in double labeling conditions and in the absence of opsin expression. Second, we have tested the in vitro photo-stimulation of CA1 pyramidal cells using electrophysiological patch clamp recordings as a readout. This gave us an estimation of the power required to induce enough photocurrents to trigger spikes and confirmed the high expression of opsins in the CA1 pyramidal cells layer. We also quantified the probability for a given Td-Tomato-expressing cell to express a sufficient amount of opsin to be stimulated. Finally, in order to evaluate how spontaneous activity levels in Chronos-expressing neurons are affected by the imaging laser beam, we quantified the depolarization induced with respect to laser power in the raster scanning conditions used for in vivo calcium imaging.Last, in vivo large-scale calcium imaging (GCamp6s) and photo-stimulation will be combined, in the pyramidal cell layer of the CA1 dorsal hippocampus, to probe the organization of cell assemblies when stimulating a subset of cells.

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**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.08/VV60

**Topic:** I.04. Physiological Methods

**Support:** Pisanello F, Pisano F, Bellistri E, Malgie E - European Research Council (Project MODEM, Starting Grant, GA #677683)

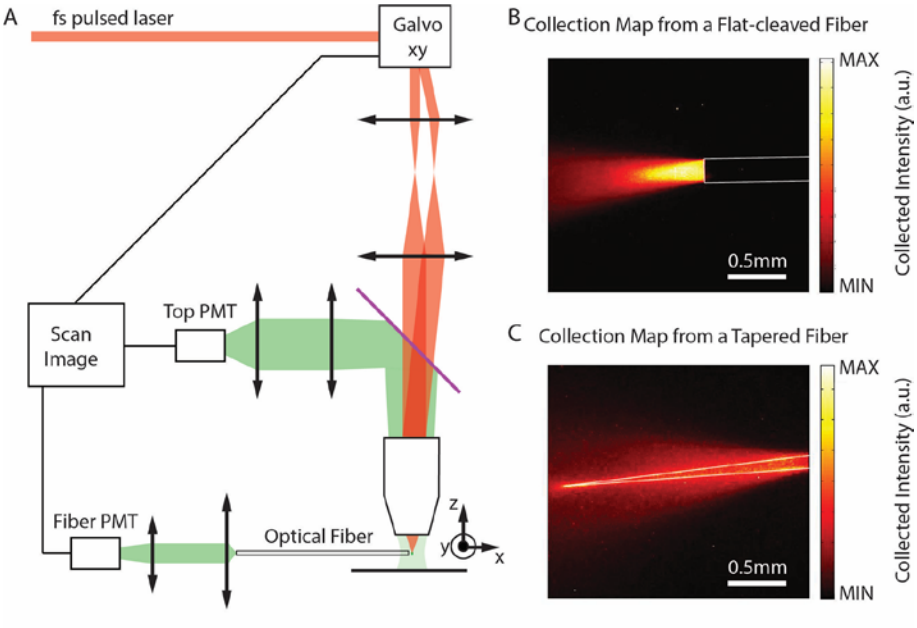
Sabatini B, De Vittorio M, Sileo L, NIH 1 U01 NS094190-01

**Title:** Direct measure of the collection diagram of fiber optics for *In vivo* photometry

**Authors:** ***F. PISANELLO**[1], H. MINSUK[3], F. PISANO[4], M. PISANELLO[2], L. SILEO[2], E. MAGLIE[2], M. DE VITTORIO, 73010[2], B. SABATINI[3]
[2]Ctr. for Biomolecular Nanotechnologies, [1]Inst. Italiano Di Tecnologia, Arnesano, Italy; [3]Dept. of Neurobiology, Howard Hughes Med. Institute, Harvard Med. Sch., Boston, MA; [4]Ctr. for Biomolecular Nanotechnologies, Inst. Italiano di Tecnologia, Arnesano, Italy

**Abstract:** The development of fiber photometry added an important building block to optogenetic methods, allowing the detection of neural signaling from genetically targeted cellular populations with simple optical fibers. In its standard implementation, an optical fiber stub is implanted into the mouse brain and used to collect luminescence from fluorescent dyes whose emission intensity is proportional to neural activity. However, although fiber photometry is rapidly diffusing among neuroscientists, there is still a considerable lack of knowledge on light collection performances of the different tools available for fiber optic neural interfaces.
We present an easy-to-implement and multipurpose method to measure collection diagrams of fiber photometry devices. It is based on the optical path in Fig.1. A 2-photon microscope generates fluorescence within a fluorescein droplet in which the device is inserted. The excited fluorescence simulates an omnidirectional point source in the sensitive area of the device. Emitted light is collected by a photomultiplier tube (fiber PMT) at the distal facet of the fiber, and by the microscope PMT to identify the position of the fluorescent spot. The signal from the fiber PMT is synchronized with a galvo scan-head moving the beam in the xy plane, resulting in a direct measurement of the collection diagram of the fiber optic. The potential of this approach relies on the fact that it can be used to evaluate light collection properties of most fiber optic devices already diffused for optogenetics. An example is given in Fig. 1B-C, displaying collection diagrams for flat-cleaved fibers and tapered optical fibers (TF) [Bioarxiv 094524], showing that TFs potentially allow for light collection from a 2mm-long segment of the taper.

Although we here discuss 2D images in a fluorescent solution, moving the microscope objective along z allows for measuring collection diagrams in 3D. Importantly, the described approach has the potential to work well also in brain slices, allowing an evaluation of the influence of tissue absorption and scattering on light collection.




**Disclosures:** **F. Pisanello:** None. **H. Minsuk:** None. **F. Pisano:** None. **M. Pisanello:** None. **L. Sileo:** None. **E. Maglie:** None. **M. De Vittorio:** None. **B. Sabatini:** None.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.09/VV61

**Topic:** I.04. Physiological Methods

**Support:** Johns Hopkins University Mann fund

**Title:** Frequency-agile, low-intensity, broadband ultrasonic array as a brain computer interface technology for improving neurological health

**Authors: S. W. LANI**, A. P. ROSENBERG, S. F. MAGRUDER, *G. M. HWANG
Johns Hopkins Univ. Applied Physics Lab., Laurel, MD

**Abstract: Background**: The skull is a complex medium that causes phase aberrations in transcranial ultrasound which can limit the focusing resolution of low-intensity

ultrasound.**Objective**: Determine whether time-reversal broadband ultrasonic transducer arrays can focus ultrasound through high-fidelity skull diploe layer adaptively with frequency selectivity between 0.5 and 10 MHz. **Methods**: Analytic methods were used to validate simulation results from k-Wave pseudo spectral time domain (PSTD) solver. A three-layer skull was modeled at three different diploe widths including 1.8, 4.6, and 2 mm. Time-reversal focusing was implemented for simulated arrays of varying apertures and bandwidth. **Results**: We achieved spatial resolution of 0.6 mm x 0.6 mm at greater than 8.4 mm depth, showing demonstrated improvement using an array with a larger bandwidth compared with state-of-the-art focusing. **Conclusions**: Simulation results suggest that a broadband ultrasonic array has the potential to perform real-time, steerable stimulation at an unprecedented small focal volume thru skull. This opens up applications on the use of low-intensity, frequency-agile, ultrasound for non-invasive treatment of neurological disorders (e.g., insomnia, anxiety, depression, post-traumatic stress disorder, and attention deficit hyperactivity disorder) and the potential for neurofeedback to accelerate learning of cognitive and motor skills to assist with rehabilitation.

**Disclosures: S.W. Lani:** None. **A.P. Rosenberg:** None. **S.F. Magruder:** None. **G.M. Hwang:** None.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.10/VV62

**Topic:** I.04. Physiological Methods

**Support:** Allen Institute for Brain Science

**Title:** Wavefront engineered multiphoton microscopy for functional imaging of mouse visual cortex during visual behavior

**Authors: *R. LIU**[1], N. BALL[2], J. BROCKILL[2], S. NISHIWAKI[2], A. STEGER[2], D. SULLIVAN[2], C. SLAUGHTERBECK[2], C. FARRELL[2], J. LECOQ[2], P. SAGGAU[2]
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Allen Inst. for Brain Sci., Seattle, WA

**Abstract:** Large-scale recording of cortical neural activity in awake and behaving animals is essential to understand the neural correlates of behavior. Wavefront-engineered multiphoton microscopy, combining spatial light modulator-based adaptive optics, multiplane/volume imaging, and three-photon fluorescence excitation, is a compelling approach to monitor such neural activity with cellular and even synaptic resolution at unprecedented recording depths. However, this approach contains several technical hurdles. First, such an integrated microscopy platform requires strict optical conjugation of scanners and wavefront correction devices to the back focal plane of the microscope objective. Second, all the microscope optics need to allow a

wide excitation wavelength range, i.e., from 900 nm to over 1300 nm. Last, the mechanical configuration of such a microscope has to be compatible with an experimental setting for visual behavior studies. We will report on our recent advances in developing a microscope platform for functional imaging of the visual cortex in head-fixed animals with eye tracking and behavior monitoring.

**Disclosures: R. Liu:** None. **N. Ball:** None. **J. Brockill:** None. **S. Nishiwaki:** None. **A. Steger:** None. **D. Sullivan:** None. **C. Slaughterbeck:** None. **C. Farrell:** None. **J. Lecoq:** None. **P. Saggau:** None.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.11/VV63

**Topic:** I.04. Physiological Methods

**Title:** Medium-retaining Petri dish inserts to grow and image miniaturized cultured cells

**Authors: *L. KIEDROWSKI**[1,2], A. FEINERMAN[3]
[1]Dept. of Biol. Sci., Univ. of Illinois At Chicago, Chicago, IL; [2]Spot Cells LLC, Chicago, IL; [3]Dept. of Electrical & Computer Engin., Univ. of Illinois at Chicago, Chicago, IL

**Abstract:** We demonstrate that when culture medium is even briefly (one second) removed from cells (neurons, astrocytes, and HEK-293 cells) the cellular $Ca^{2+}$ homeostasis becomes acutely destabilized. This data also implies that the cells grown on plain coverslips experience similar $Ca^{2+}$ homeostasis destabilization when these coverslips are removed from culture media and installed on microscope stages. We show that a custom sample holder can avoid this destabilization by keeping cells continuously immersed during observations. The background for this work is as follows. In experiments involving superfusion, differential interference contrast and intracellular fluorescence imaging, the cells of interest are typically plated on glass coverslips submerged in culture media in Petri dishes. Prior to these experiments, coverslips must be transferred from a Petri dish to a dedicated superfusion-optimized coverslip holder installed on a microscope stage. The problem is that the cells are exposed to air during the transfer. This exposure and the subsequent mechanical stress associated with re-submerging the cells in medium can affect cellular $Ca^{2+}$ homeostasis. To avoid this potential problem, a special Petri dish insert has been designed and constructed. This insert features a medium-retaining well with a glass bottom. The shape of this well is optimized for superfusion. When the insert is removed from a Petri dish, the culture medium is retained in the well. This property allows the cells to stay submerged at all times during the experiment. In this project, these inserts were used to test the impact of a transient medium removal from the well (an equivalent of a transient coverslip removal from the medium) on intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_i$) in miniaturized

cultures of primary murine cortical neurons and astrocytes and HEK-293 cells. The cultures were plated in the inserts and $[Ca^{2+}]_i$ was monitored using fura-2. The medium was removed from the well for only one second. In all cells, this maneuver induced a micromolar $[Ca^{2+}]_i$ spike. While in neurons this spike was caused by a $Ca^{2+}$ influx, in astrocytes and HEK-293 cells, it was caused by a $Ca^{2+}$ release from intracellular stores. After the spike, a subpopulation of neurons, astrocytes, and HEK-293 failed to restore low $[Ca^{2+}]_i$ promptly. Notably, in 24% of the astrocytes, the spike triggered $[Ca^{2+}]_i$ oscillations. Since the cells growing in the medium-retaining inserts remain constantly submerged, one can use these inserts to avoid disturbing basal $[Ca^{2+}]_i$ levels in the imaged cells.

**Disclosures: L. Kiedrowski:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ownership interest in Spot Cells LLC. **A. Feinerman:** None.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.12/VV64

**Topic:** I.03. Anatomical Methods

**Title:** Electrical and biocompatibility properties of different soft intra-cortical implant designs

**Authors: *P. VILLARD**[1], J.-M. MAYAUDON[1], C. ZENGA[1], A. QUESNEL-HELLMANN[1], L. ROUSSEAU[2], B. YVERT[1], G. PIRET[1]
[1]Braintech Lab., INSERM U1205, Grenoble cedex 09, France; [2]Esiee-Paris, Noisy le grand, France

**Abstract:** Neuroengineering more efficient neural interfaces is crucial to develop better clinical rehabilitation solutions and for neural network exploration. Most of current intra-cortical implants are stiff and generate mechanical strain that results in complex cellular responses and instabilities in neural signal recording. Designing soft intra-cortical neural implant with a high density microelectrode array has therefore become essential to faithfully record several neural units overtime and to facilitate for instance, brain computer interface performances and the study of memory and plasticity. We developed a soft SU-8 polymer neural implant with 64 nanostructured gold 20µm electrodes and vary the design of the 2mm deep intra-cortical part of the implant. Leads were either 50µm, 20µm or 11µm wide with a straight or a wavy shape. We then evaluated the impact of different designs on electrical properties of the implant. In vivo biocompatibility tests in rodents were performed and astrocytes, microglia and cell density were analysed around the different implant lead types.

**Disclosures:** **P. Villard:** None. **J. Mayaudon:** None. **C. Zenga:** None. **A. Quesnel-Hellmann:** None. **L. rousseau:** None. **B. Yvert:** None. **G. Piret:** None.

**Poster**

**528. Optical Physiology, Electrodes, and Light Shaping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 528.13/VV65

**Topic:** B.04. Ion Channels

**Support:** NIH Grant R37AA009986

NIH Grant T32AA007474

**Title:** Effects of drugs of abuse on channelrhodopsin 2 kinetics

**Authors: *D. A. GIOIA**[1], W. N. WAYMAN[2], M. XU[5], C. RIEGEL[3], C. M. REICHEL[4], J. J. WOODWARD[4]
[1]Inst. of Psychiatry, [2]Neurosci., [4]Neurosciences, [3]Med. Univ. of South Carolina, Charleston, SC; [5]Med. Univ. South Carolina, Charleston, SC

**Abstract:** Channelrhodopsins are light activated ion channels and have been extensively used in neuroscience research over the past decade to probe the function of genetically defined neuronal populations and distinct neural circuits with high temporal and spatial precision. The widely used Channelrhodopsin 2 variant (ChR2) is an excitatory opsin that undergoes conformational changes in response to blue light, allowing non-selective passage of protons and cations across the plasma membrane. In the addiction neuroscience field, opsins such as ChR2 provide a means to disambiguate the overlapping circuitry involved in mediating the reinforcing and aversive effects of drugs of abuse as well as determine the plasticity that occurs in these circuits during the development of dependence. Although ChR2 has been widely used in animal models of drug and alcohol self-administration, it is not known whether drugs of abuse have acute actions on ChR2 function that may confound its use. Considering that many drugs of abuse directly alter the function of other ion channels, it is important to determine whether ChR2-mediated currents are also directly modulated by these drugs. In this study, we performed whole-cell electrophysiological recordings in HEK293 cells expressing the commonly used ChR2(H134R) variant and examined the effects of various drugs of abuse on light-induced currents. Cells were voltage-clamped at -60 mV and subjected to a series of brief (5 msec; 1 Hz) blue light pulses (470 nm) before, during and after exposure to each drug. The amplitude and rise time of light-activated currents in ChR2(H134R) expressing HEK cells were insensitive to effects of ethanol at physiologically relevant concentrations but were minimally affected by ethanol at concentrations of 100 and 300 mM. Similarly, we found no differences in the amplitude or rise time of ChR2-mediated currents in the presence of 10 or 30 µM nicotine, 30 µM cocaine or 3

mM toluene. There was also no effect of these drugs on the desensitization of ChR2 currents that occurs during repetitive stimulations. Together, the results from this study suggests that biologically relevant concentrations of commonly studied drugs of abuse do not significantly affect the function of ChR2 providing further validation for its use in substance abuse studies. We further examined the effects of various other chemicals commonly used in research and found that 10mM gadolinium chloride as well as 5µM tetrodotoxin significantly inhibited ChR2 mediated currents while 10mM magnesium chloride did not. These results indicate that appropriate control experiments should be used when designing experiments with optogenetic tools.

**Disclosures:** **D.A. Gioia:** None. **W.N. Wayman:** None. **M. Xu:** None. **C. Riegel:** None. **C.M. Reichel:** None. **J.J. Woodward:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.01/VV66

**Topic:** I.04. Physiological Methods

**Support:** HR0011-15-2-0017

**Title:** Biomarkers for fiber recruitment within the vagus nerve and impact of cuff geometry

**Authors:** ***J. BUCKSOT**[1], J. RILEY[2], K. LOERWALD[2], K. RAHEBI[2], M. RIOS[2], M. KILGARD[2], R. RENNAKER[2], S. HAYS[2]
[1]Bioengineering, [2]Univ. of Texas At Dallas, Richardson, TX

**Abstract:** Vagus nerve stimulation (VNS) is used for a variety of applications including epilepsy, major depressive disorder, and recovery from neurological injury. Optimizing vagus nerve activation on an individual basis could have significant impact on clinical outcomes given the variety of VNS applications and patient variability. Here we investigate two possible strategies for optimizing the delivery of VNS: use of biomarkers to determine optimal stimulation parameters and changes in nerve cuff geometries. SpO2 and heart rate served as our biomarkers of thick A and thinner B fiber recruitment, respectively. Changes in SpO2 and heart rate were measured in anesthetized animals in both acute and chronic conditions. The magnitude of change in spO2 and/or heart rate was determined as a function of the stimulation parameters (current, frequency, pulse width, and train duration). In addition, multiple cuff geometries were tested to determine how the degree of nerve encompassed within a circumferential electrode affected the fiber recruitment function. Each cuff geometry was tested in an acute, anesthetized preparation on the rat sciatic nerve and the force of gastrocnemius muscle contraction was measured to determine the amount of fiber recruitment. Consistent with our understanding of A

and B fiber thresholds, preliminary results showed drops in SpO2 starting at low currents (~200µA) and drops in heart rate starting at higher currents (~1600µA) in the acute condition. There was an increase in both thresholds observed in the chronic condition. Additionally, results indicated that the steepness of the recruitment function was dependent on the amount of nerve encompassed within the electrode. Covering a greater portion of the nerve resulted in steeper recruitment. This information will be applied in upcoming experiments in which the recruitment function and fiber type activation will be tailored to the experimental conditions with the goal of improving behavioral outcomes dependent on VNS plasticity.

**Disclosures: J. Bucksot:** None. **J. Riley:** None. **K. Loerwald:** None. **K. Rahebi:** None. **M. Rios:** None. **M. Kilgard:** None. **R. Rennaker:** None. **S. Hays:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.02/VV67

**Topic:** I.04. Physiological Methods

**Support:** Frank Quick Research Innovation Fellowship

Draper Laboratory Fellowship

**Title:** Electrochemical neuromodulation using cuff electrodes modified with ion-selective membranes

**Authors: *M. T. FLAVIN**[1,2], J. HAN[1], D. K. FREEMAN[2]
[1]MIT, Cambridge, MA; [2]Draper Lab., Cambridge, MA

**Abstract:** Developing precise and effective means of modulating the nervous system is a major challenge in neural prosthetics. Our approach is to perform localized chemical modulation by polarizing electrodes modified with ion-selective membranes (ISM), creating ion-concentration polarization (ICP). With this physical process, the interstitial concentrations of selected ions can be manipulated in a spatially and temporally precise manner. Here, we report the design and testing of a prototype peripheral nerve cuff electrode with ISM-modified contacts for the purposes of ICP-based neuromodulation. We fabricated a silicone/carbon multi-contact cuff electrode with $Ca^{2+}$ or $K^{+}$ -selective ISM formulations drop-cast onto one of the contacts (depicted in Figure 1). Characteristic behavior was simulated using a Nernst-Planck-Poisson (NPP) model in COMSOL Multiphysics, producing results shown in Figure 2. In order to identify defects and evaluate long-term stability, electrode impedances of coated and uncoated contacts were determined using electrochemical impedance spectroscopy (EIS) (see Figure 3). The ISM cuff electrodes were ultimately used to test the impact of electrochemical

neuromodulation in an *ex vivo* frog sciatic nerve model. In the preliminary results shown in Figure 4, we see that cathodic current applied at the $Ca^{2+}$-ISM contact resulted in lowering of excitation thresholds, consistent with neurons being subjected to depletion of extracellular $Ca^{2+}$. The original excitation threshold was restored following a brief recovery period. Similar experiments with modulation of other ions (e.g. $K^{+}$) will be investigated in the future. As a fully realized technology, an ISM cuff electrode could potentially be used to lower the stimulus energy required to elicit muscle activation (via $Ca^{2+}$ manipulation), or block aberrantly firing nerves that characterize neuropathic pain disorders (via $K^{+}$ manipulation). Furthermore, ISM-based stimulation could eventually be applied beyond the peripheral nervous system to address neurological and psychiatric disorders in the brain.

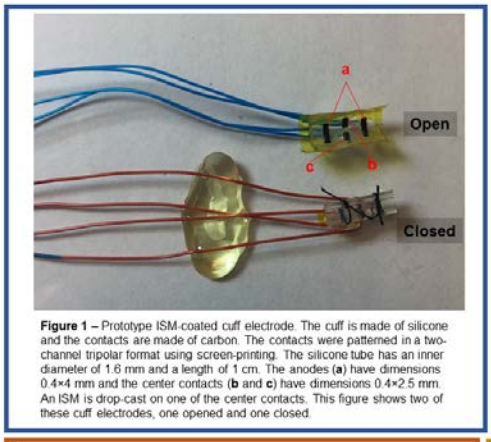



**Figure 1 –** Prototype ISM-coated cuff electrode. The cuff is made of silicone and the contacts are made of carbon. The contacts were patterned in a two-channel tripolar format using screen-printing. The silicone tube has an inner diameter of 1.6 mm and a length of 1 cm. The anodes (**a**) have dimensions 0.4×4 mm and the center contacts (**b** and **c**) have dimensions 0.4×2.5 mm. An ISM is drop-cast on one of the center contacts. This figure shows two of these cuff electrodes, one opened and one closed.

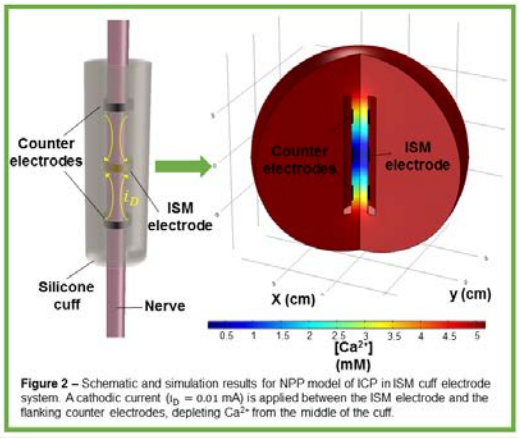



**Figure 2 –** Schematic and simulation results for NPP model of ICP in ISM cuff electrode system. A cathodic current ($I_D$ = 0.01 mA) is applied between the ISM electrode and the flanking counter electrodes, depleting $Ca^{2+}$ from the middle of the cuff.

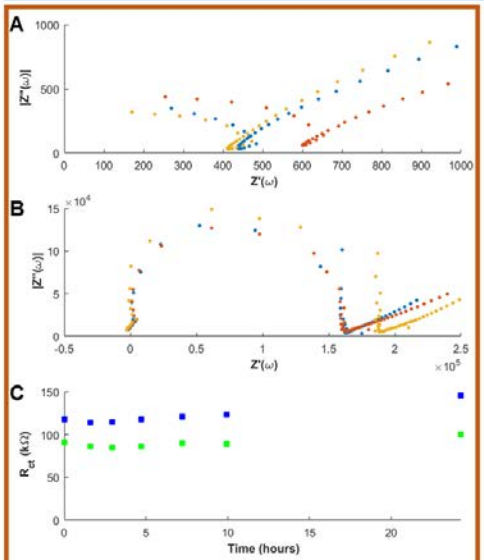



**Figure 3 –** EIS performed on several carbon/ISM cuff electrodes in PBS with Ag/AgCl reference and large-area carbon paper counter (10 mV peak-to-peak, 100 kHz -1 Hz). **A** Nyquist plot showing results with one of the anodes as primary electrode for three separate devices. The charge-transfer resistance estimated from the diameter of the semi-circle is $R_{CT} \approx 400-600\ \Omega$. **B** Nyquist plot showing results with carbon/ISM electrode as primary for three separate devices. The charge-transfer resistance estimated from the diameter of the semi-circle is $R_{CT} \approx 160-190\ k\Omega$. **C** Charge-transfer resistance measured over the course of 24 hours for two different carbon/ISM electrodes, determined from the diameter of the semi-circle on the EIS Nyquist plot.

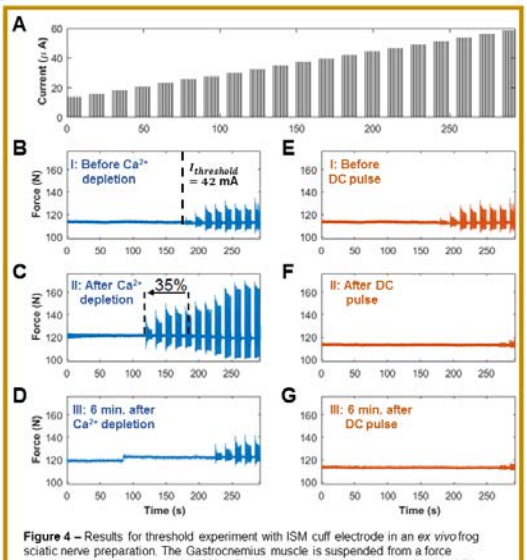



**Figure 4 –** Results for threshold experiment with ISM cuff electrode in an *ex vivo* frog sciatic nerve preparation. The Gastrocnemius muscle is suspended from a force transducer while the nerve, with ISM cuff electrode attached, is immersed in amphibian Ringer's solution. The threshold searching procedure is to apply a ramped train of pulses, recording the smallest amplitude to produce a muscle contraction. During Phase I, the threshold is determined without any $Ca^{2+}$. During Phase II, the threshold is determined immediately after either $Ca^{2+}$ depletion from ISM or DC pulse from uncoated cathode. During Phase III, the threshold is determined after 6 min. of equilibration. **A** Waveform for ramped pulse train. **B-D** Output of force transducer for each respective phase using the ISM electrode. The pulse train ranged from 13.5 µA to 58.5 µA, and the ISM depletion current had a magnitude of 20 µA. **E-G** Output of force transducer for each respective phase using an uncoated cathode (control). The pulse train ranged from 15 µA to 65 µA, and the DC pulse had a magnitude of 20 µA.

**Disclosures:** **M.T. Flavin:** None. **J. Han:** None. **D.K. Freeman:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.03/VV68

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Targeting of DREADD expressing vectors into cytoarchitecturally different monkey brain regions at high penetrance

**Authors: *W. LERCHNER**, M. A. G. ELDRIDGE, D. MILLER, J. M. FREDERICKS, D. ROSE, V. DER MINASSIAN, V. D. COSTA, B. B. AVERBECK, B. J. RICHMOND
LN/NIMH, NIH, Bethesda, MD

**Abstract:** To make use of chemogenetic tools, such as DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), for behavioral studies in old-world monkeys, it is necessary to express receptor-encoding genes via injections of a viral vector. Here we show that we can use mechanically guided injections of lentivirus (LV), and in some cases adeno-associated virus (AAV), to express a DREADD gene with high neuronal penetrance, in cytoarchitecturally different regions. We analyze expression in three structures: the amygdala – a large, multi-nucleus structure; the tail of the caudate nucleus (ToC) – a small region deep in the brain adjacent to the lateral ventricles; and cortex – a thin laminar structure.
$Mn^{2+}$ can be used for post-surgery verification of injection sites and successful infusion by creating an MRI hypersignal lasting hours to days after surgery. Here we show that the infectious titer of LV containing 10mM of $MnCl_2$ is stable *in vitro* for at least 6 hours. To test *in vivo*, 5µl lentivirus mixed with concentrations of $MnCl_2$ from 0.1, 1.0, and 10mM was injected into monkey cortex, all resulting in a detectable MRI hypersignal. Histological visualization of DREADD expression showed that coverage and penetrance were not affected by addition of $MnCl_2$. In the same monkey, injection of 5µl AAV2 into cortex yielded a four-fold larger expression volume, but the percentage of expressing neurons in the covered area was markedly lower than with LV. We then compared injections of both LV and AAV2 containing 1mM MnCl2 into the ToC. The $Mn^{2+}$ MRI hypersignal was centered at the estimated position of the needle tip on the histological sections. Both LV and AAV resulted in penetrance of up to 100% in the ToC.
In the amygdala, we compared a single 80µl injection of lentivirus with four individual 20µl injections, spaced 2mm apart. The 80 µl injection yielded an average of 75% penetrance over a volume of about $50mm^3$ compared to 55% average penetrance and $65mm^3$ coverage for the four 20µl injections. However, in the 80µl injection nearly 6% of the expressing area also showed a complete shut-down of the neuronal marker NeuN, likely due to toxic overexpression of the DREADD gene, something not seen in the 20µl injections. While there were a few gaps in expression in between the four injections spaced 2mm apart, encouragingly, cell counts indicated

that a majority of expression regions had neuronal penetrance above 90%. From these results, we project that covering the one entire amygdala (approx. 300 $mm^3$) at >90%, a 1.5mm grid of 14 - 15 injections of 20μl each will be required.

**Disclosures:** **W. Lerchner:** None. **M.A.G. Eldridge:** None. **D. Miller:** None. **J.M. Fredericks:** None. **D. Rose:** None. **V. Der Minassian:** None. **V.D. Costa:** None. **B.B. Averbeck:** None. **B.J. Richmond:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.04/VV69

**Topic:** I.04. Physiological Methods

**Support:** NIH Grant EY019679

NIH Grant EY025542

**Title:** A deep-brain multi-wire electrode array and cartridge-based implantation system for high-resolution recording and stimulation with demonstration as a visual prosthesis

**Authors: *N. J. KILLIAN**, J. S. PEZARIS
Neurosurg., Massachusetts Gen. Hosp., Boston, MA

**Abstract:** We have developed a multi-wire electrode array (brush-style microwire bundle) and accompanying implantation system for high-resolution physiology and therapeutic stimulation of deep brain structures. The implantation system is suitable for acute, semi-chronic, and chronic applications. The device was implanted bilaterally in the lateral geniculate nucleus (LGN) in one monkey (Macaca mulatta), for one year, as part of the first-generation prototype of a thalamic visual prosthesis.

The electrode array comprises a bundle of 64 platinum-iridium microwires (38 micron O.D.) mated with miniature connectors and sheathed in a polyimide tube, with a second, thick polyimide inner guide tube and a third stainless steel outer guide tube. The inner guide tube is manually positioned to the desired depth above the target structure. The outer guide tube is used to penetrate the dura and is reversibly secured using wax or silicone. The array and guide tubes are all securely located in a cartridge enclosed by a peel-away carrier. Cartridges mate with a positioning rod mounted to a standard microdrive and are readily interchangeable during a procedure. The positioning rod and carrier provide an access port for all array sites and can be adapted to common hydraulic microdrive positioning systems.

To demonstrate the system, wire tips of the bundle were cut to match the geometry of the LGN and then sonicoplated with platinum black in order to reduce the impedance for stimulation

(median 18 kOhm at 1 kHz, 2 weeks post-implant). We first verified the target location using a single-electrode cartridge, and then changed to a bundle-electrode cartridge for implantation. Intraoperative single- and multi-unit recordings were made from the bundle electrode array while the animal was awake and performing a receptive field mapping task. Using the receptive field locations, bundle positioning was fine-tuned with the microdrive before sealing the device in place within titanium recording cylinders. Distinct artificial visual percepts, known as phosphenes, were evoked by stimulating individual wires and mapped with a saccade-based task. To examine the animal's perception through patterned stimulation, phosphenes were simultaneously activated to represent either the letter C or W, artificially presented at a size corresponding to a visual acuity of logMAR 2.2. The animal successfully discriminated the artificially presented letters on 60% of trials ($p < 0.05$, binomial test), consistent with our prior studies using a virtual reality simulation. Second-generation higher channel count implants are in preparation.

**Disclosures:** **N.J. Killian:** None. **J.S. Pezaris:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.05/VV70

**Topic:** I.04. Physiological Methods

**Support:** Draper Laboratory R&D Award

**Title:** Going wireless: Validation of a novel neurostimulation technology in a conditioned place preference task

**Authors: *L. Y. MAENG**[1], M. F. MURILLO[2], M.-C. LO[3], D. K. FREEMAN[4], M. R. MILAD[5], A. S. WIDGE[2]
[1]Dept. of Psychiatry, Massachusetts Gen. Hospital/Harvard Med. Sch., Charlestown, MA; [2]Psychiatry, Massachusetts Gen. Hosp., Charlestown, MA; [3]Psychiatry, Massachusetts Gen. Hosp., charlestown, MA; [4]Draper Lab., Cambridge, MA; [5]Psychiatry, Harvard Med. School, Mass. Gen. Hospital,, Boston, MA

**Abstract: Background:** Deep brain stimulation (DBS) technologies have gained increasing interest in the treatment of not only neurological but also psychiatric disease due to growing evidence of aberrant functioning within brain circuits and connectivity in a number of psychopathologies. DBS can target these specific dysfunctioning brain areas, and with its increased use, there is a need for improved devices. Electrophysiological tools are widely used and tested in rodent models, and here we aimed to validate a novel wireless neurostimulator device, the eParticle (EP), using rewarding medial forebrain (MFB) stimulation in a conditioned

place preference (CPP) paradigm. **Methods:** Adult male Sprague Dawley rats received an implantation of a Plastics One electrode into the MFB on one side of the brain and the wireless e-particle on the other side, counterbalancing for hemisphere. Each animal was implanted with both the commercial electrode and wireless EP to enable within-subject comparisons of effective stimulation. After recovery, all animals were tested for conditioned place preference in an open field with a designated quadrant as the stimulation quadrant. Place preference was measured by the percentage of time spent in the stimulation quadrant during 15-minute sessions in an open field. E-particle stimulations were administered via transmitter coils at (monophasic, 50 Hz, 0.1ms pulse width, 0.25s pulse duration). Wired stimulation parameters (biphasic, 350 uA, 160Hz, 0.1ms pulse width, 0.5s pulse duration) were determined by confirmation of rewarding behavior in a bar press self-stimulation task. **Results:** Animals that received EP stimulation of the MFB increased the amount of time spent in the stimulation quadrant, significantly during stimulation ($p \leq 0.05$) and trending towards significance during the post-stimulation test session ($p \leq 0.05$) when the animals were not receiving any stimulation. These EP effects were not as robust as with wired electrodes. Nevertheless, wireless EP stimulation was capable of achieving the rewarding effects of MFB stimulation, suggesting that it may still be a useful and effective tool for brain stimulation. **Conclusions:** These initial results appear to be promising despite the limitations of the EP stimulation parameters compared to wired stimulation. Future studies should assess the efficacy of EP neurostimulation in other behavioral tasks with known neurocircuitry.

**Disclosures: L.Y. Maeng:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Draper Laboratory. **M.F. Murillo:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Draper Laboratory. **M. Lo:** None. **D.K. Freeman:** None. **M.R. Milad:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Draper Laboratory. **A.S. Widge:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Draper Laboratory.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.06/VV71

**Topic:** I.04. Physiological Methods

**Title:** Simultaneous monitoring of changes in neuronal oscillations and behavior of unrestrained animals: A novel technique in neuropharmacology

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**Abstract:** Compounds are screened in variety of animal models during preclinical evaluation; however they often suffer with the limitation of translatability to human. Researchers across globe are in constant search of animal models which will help them in addressing this problem. Electroencephalography (EEG) is one of the preclinical models which show characteristics with great similarities across species. Therefore, drug-induced changes in EEG characteristics in animals may be used to predict central activity of drugs in humans. If the relation of EEG and behavior is established / proved in animals, this approach will be more meaningful and beneficial to evaluate compounds acting on sleep, cognition, locomotor activity. In the current investigation animals were implanted with a telemetric device having two bio-potential electrodes capable of measuring EEG from two brain regions simultaneously. After surgical recovery, animals were subjected for exploration of open field and neuronal oscillations from same animal were simultaneously monitored. Similarly, animals were subjected for the simultaneous object recognition task in parallel to the EEG monitoring. In open field, treatment with psychostimulants produced increase in locomotor activity with simultaneous decrease in theta, alpha and beta power densities. Similarly, during novel object exploration, acetylcholineesterase inhibitors like donepezil increased the power in theta frequency during exploration of novel object. The current model demonstrated the simultaneous monitoring of animal behavior and the changes in neuronal oscillations during different behaviors. Simultaneous monitoring of these parameters in the early stages of discovery program will increase the chances of translatability during development of drugs.

**Disclosures:** **S. Daripelli:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **C. Tirumalasetty:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **R. Medapati:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.07/VV72

**Topic:** I.04. Physiological Methods

**Support:** NIH RO1 RO1MH101218

ARO W911NF-12-1-0594

KAVLI INSTITUTE OF BRAIN SCIENCE

**Title:** Stable, high-throughput giga-seal intracellular recordings *In vivo* using biomimetic nanopipettes

**Authors: *K. JAYANT**[1], J.-M. Y. CARRILLO[4], A. HARTEL[2], M. WENZEL[3], S. SHEKAR[2], V. MEUNIER[5], O. SAHIN[3], R. YUSTE[3], K. L. SHEPARD[2]
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**Abstract:** Whole-cell recordings *in vivo* are a key technique for neuroscience; yet, technical difficulties have precluded their more widespread use. First, the mechanical mismatch between the neuron and stiff patch pipette often leads to recording instabilities in the presence of motion. Second, patch pipettes require the continuous application of pressure while navigating through the brain to avoid clogging and exhibit increased access resistance with depth. Both of these challenges lead to suboptimal recordings and low experimental throughput. There is, therefore, a need for small, flexible, and minimally invasive intracellular electrodes that can enable high throughput, high-signal-to-noise-ratio (SNR) recordings *in vivo*. To address this challenge, we recently introduced quartz nanopipettes (inner diameters ~15nm) as direct electrical interfaces to dendritic spines *in vitro* [1], and rendered them flexible for targeted recordings *in vivo* [2]. Although, we achieved repeatable high-SNR recordings in both anaesthetized and awake animals, the seal resistance between the nanopipette and neuron was variable (~500-800MΩ), and recordings were not completely immune to movement. Here, we introduce "biomimetic nanopipettes" - lipid-coated electrodes that form spontaneous giga-seals with neuronal membranes. We first measured the nanopipette seal resistance *in vitro* by obtaining the input resistance of the neuron before and after lipid-coated nanopipette entry and found seal resistances ≥1.2GΩ. This was accomplished with simultaneous whole-cell patch and nanopipette recordings from the same cell. We corroborated this interaction through detailed molecular dynamic (MD) simulations, and found that the neuronal membrane and lipid-coated nanopipette form a new separate bilayer during entry - the basis for giga-seal formation. This interaction is found to be dependent on lipid grafting density and uniformity. We demonstrate that biomimetic nanopipettes routinely permit stable (~1hr), high-throughput (10 cells/nanopipette), and high-SNR intracellular recordings from awake head-fixed mice running on a wheel.
[1] K. Jayant et.al., *Nat. Nanotech*, **12**, 335-342 (2017)
[2] K. Jayant et. al., (*Submitted*)
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**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

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**Program#/Poster#:** 529.08/VV73

**Topic:** I.04. Physiological Methods

**Support:** The ERC Interimpact project

The Hungarian Academy of Sciences

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The National Brain Research Program, Hungary

**Title:** Triple-microdrive assembly for simultaneous juxtacellular neural recording and labeling in freely moving rats

**Authors: *R. G. AVERKIN**, G. TAMAS
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**Abstract:** We present a microdrive assembly for three pipettes to be used in simultaneous juxtacellular recording and labeling of cortical neurons in freely moving rats. The assembly combines three modified Korshunov type (Korshunov, 1995) microdrives and is capable of independent manipulation of individual glass pipettes filled with 0.5M NaCl solution with 1.5-2.0% Neurobiotin. Each microdrive is tilted at 7 degrees relative to the central axis of the overall assembly axis and has a 12 mm advancing range with 350 μm per revolution. The assembly can be secured to a holding platform to target closely spaced neurons in supragranular layers of the same cortical area (>0.36 $mm^2$). During surgery, a chamber (ID=4.5mm; height =2mm) is attached by acrylic cement to the skull above the agar-coated surgery hole (ID=2.3mm) with the dura left intact. The microdrive assembly preloaded with the three pipettes is placed on to the holding platform and fixed by a single screw on the awake animal, thus the installation procedure does not require pre-anesthesia. The whole construction including the acrylic cement weighs 4.9 g. In initial experiments, we successfully used the assembly for simultaneous juxtacellular recordings and anatomical labeling of three neurons including interneurons and pyramidal cells in freely moving rats during awake state and natural sleep for up to 20 minutes. When searching for a cell on one channel, juxtacellular spikes remained unaffected on the other two channels. Differences were readily identified during the same epochs in the firing of simultaneously recorded pyramidal-pyramidal and pyramidal-interneuron cell pairs and triplets.

**Disclosures: R.G. Averkin:** None. **G. Tamas:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.09/VV74

**Topic:** D.01. Sensory Disorders

**Support:** KAKENHI Grant Numbers JP16K01408

**Title:** Major depression index derived from the relationship between hurst exponent and zero crossing rate in voice

**Authors: *S. SHINOHARA**[1], Y. OMIYA[2], M. NAKAMURA[1], M. HIGUCHI[1], N. HAGIWARA[2], T. TAKANO[2], H. TODA[3], T. SAITO[3], M. TANICHI[3], A. YOSHINO[3], S. MITSUYOSHI[1], S. TOKUNO[1]
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**Abstract:** The hypothesis that depression is caused by decreasing monoamines such as serotonin and dopamine in the brain has been proposed. These neurotransmitters are known to affect mood. On the other hand, as you can see from the fact that you can recognize the other's emotion even on the phone, the change in mood appears in the voice. From the above viewpoint, we have studied indicators that can detect depression from speech. In this report, we propose a new depression index based on the relationship between zero crossing rate (ZCR) and hurst exponent (H) of speech signal.ZCR is an index often used in the field of voice activity detection, which represents the rate at which the signal changes from positive to negative and vice versa. On the other hand, H is an indicator often used in the analysis of stock prices and indicates how far away from the initial position with time, and in theory it is H = 0.0 for white noise and H = 0.5 for brown noise. We have found that there is a negative correlation between ZCR and H. The speech signal is divided into small sections, and ZCR and H are calculated in each section. We derived a new major depression index (MDI) from these aggregated data. In this study we collected the voices from both healthy individuals and patients with major depression, reading 17 fixed phrases (N = 43 and N = 25 respectively). The values of MDI were calculated from the voices. The average values of healthy subjects and major depressed patients were -0.251 ± 0.080 and -0.360 ± 0.076, respectively. As a result of the t test, there was a significant difference between them (p = 5.3210 E - 07). To evaluate the performance of MDI in discriminating between patients and healthy individuals, we used area under the curve (AUC) in the receiver operating characteristic plot. The AUC was 0.85.For major depression patients, Hamilton Depression Rating Scale (HAMD) was conducted. The voice data of major depression patients were divided into two with HAMD score less than 14 (mild) or over 14 (severe). The MDI mean values of the mild group and the severe group were -0.313 ± 0.048 and -0.411 ± 0.068,

respectively. As a result of the t test, there was a significant difference between them (p = 0.000343). The AUC was 0.88 for the discrimination performance between mild group and severe group.Thus, it was shown that the proposed index not only distinguished between major depression patients and healthy individuals, but also a good indicator of severity.

**Disclosures:** **S. Shinohara:** None. **Y. Omiya:** None. **M. Nakamura:** None. **M. Higuchi:** None. **N. Hagiwara:** None. **T. Takano:** None. **H. Toda:** None. **T. Saito:** None. **M. Tanichi:** None. **A. Yoshino:** None. **S. Mitsuyoshi:** None. **S. Tokuno:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.10/VV75

**Topic:** I.04. Physiological Methods

**Support:** BBSRC award BB/K001817/1

Scientifica Ltd

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**Title:** Robotic automation of *In vivo* two photon targeted whole-cell patch clamp electrophysiology

**Authors: *L. A. ANNECCHINO**, A. R. MORRIS, C. S. COPELAND, O. E. AGABI, P. CHADDERTON, S. R. SCHULTZ
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**Abstract:** Whole-cell patch clamp electrophysiological recording (WCR) constitutes the best tool for high-fidelity analysis of post synaptic responses to sensorial stimuli, behavioural states and cognitive processes in healthy and pathological conditions. While in vivo patch clamp recording has recently benefited from automation, it is normally performed “blind”, meaning that throughput for sampling certain genetically and morphologically defined cell types is relatively low.
The inherent cell-type non selectivity of this technique can be overcome by combining WCR with two photon microscopy, and targeting recordings to specifically labelled individual cells or cell classes in vivo. However, combining this with robotic automation is intrinsically difficult, as micropipette penetration induces tissue deformation, moving target cells from their initial location. In particular, the precise vision-guided navigation of patch pipette to an anatomical target requires specialised skills acquired through extensive practice and training by individual operators and remains a challenging task.
In this study we describe a platform for automated two photon targeted patch clamp recording,

which solves this problem by making use of a closed loop visual servo algorithm. Our system keeps the target cell in focus while iteratively adjusting the pipette approach trajectory to compensate for tissue motion. The system automatically controls a micromanipulator, a signal amplifier, a two-photon microscope and a custom-made regulator for controlling pipette pressure. The system acquires images of fluorescently labelled cells, and targets for patch clamp are selected via a point-and-click graphical user interface.
We demonstrate platform validation with patch clamp recordings from a variety of cells in the mouse neocortex and cerebellum. The system was tested in both “blind” and two-photon targeted paradigms. In automatic “blind” WCR mode, when visual targeting was deactivated and therefore no cell or cell-type selectivity implemented, the success rate was 51.4%. In automatic “targeted” mode, success rate for robotic visual guided WCR targeted at fluorescently labelled cells was 19.3%. Such performances are comparable or exceed those obtained by human operators, in terms of yield, recording quality and operational speed in the absence of lengthy user training times. These results prove the feasibility of robotic targeted WCR patch clamp in vivo and establish this system as a powerful tool for automated electrophysiological experiments in the brain.

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**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

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**Program#/Poster#:** 529.11/VV76

**Topic:** I.04. Physiological Methods

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**Title:** Animal locomotion control using electrical brain stimulation on amygdala for “Go” and “Back” commands

**Authors: *Y. LEE**[1], J. LEE[2], Y. CHO[2], S. KIM[2], C. KONG[4], J. SHIN[4], C. KO[4], H. JUNG[4], J. CHANG[4], S. JUN[2,3]
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**Abstract:** There have been attempts to control animals' locomotion via electrical stimulation on brain. For this purpose, it is typical to stimulate dopamine-related reward neural pathways including medial forebrain bundle (MFB). Animals can be trained when MFB stimulation is delivered as a reward immediately after animal correctly follows the external commands such as directional cues. However, one limitation of this strategy is that training is impossible if animals fail to follow the commands because it is only for a "Go" commands. In this study, amygdale nucleus (AMY), the brain center of fear modulation, is additionally targeted for training via punishment. Electrical stimulation is applied on AMY of Sprague-Dawley rats under freely moving condition when the animal goes wrong direction after command signals for directions. All the stimulations including MFB, AMY, directional cues, are performed using a custom-made multichannel microelectrode array (tungsten, 254 μm diameter). As directional cue signals, stimulation of somatosensory barrel cortex is delivered on either of hemisphere. Three animal groups are examined depending on the strategies: 1) Group R (MFB stimulation for reward only), 2) Group F (AMY stimulation for fear only) and 3) Group B (stimulation on both MFB and AMY). The effectiveness for training is quantified by measuring the success rates based on correct directional decision making. As a result, Group B shows the highest success rate and faster training overall, compared to the other groups. This study indicates that the behavioral training using both reward and fear stimulations is more effective for locomotion control than using either of the stimulations.

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**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.12/VV77

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NSC 101-2410-H-002-082-MY3

MOST105-2420-H-006-004-MY2

MOST 105-2410-H-002-051

**Title:** Fear conditioning altered BOLD responses in dexmedetomidine sedated rats

**Authors: *K.-H. CHEN**[1], D.-Y. CHEN[2], K. LIANG[3]
[1]Dept. of Psychology, Natl. Taiwan Univ., Taipei, Taiwan; [2]Dept Psychology, Natl. Cheng Kung Univ., Tainan, Taiwan; [3]Natl. Taiwan Univ., Taipei, Taiwan

**Abstract:** In search for neural changes altered by learning, recording at specific sites often confined detection of a distributed neural network subserving the engram. While functional MRI may provide a potential *in vivo* measurement of the whole brain activity, head motion has prevented its use in rodent studies. To curtail this problem, we developed a protocol in which rats acquired light-shock association under dexmedetomidine sedation (0.1 mg/kg/hr, s.c.) and subsequently expressed their memory of fear in a fear potentiation of startle (FPS) task. Behavioral results showed that an intense foot shock (1.25 mA) yielded a significant FPS response, while a weak shock (0.63 mA) yielded minimal learning that can be enhanced by pre-training injection of 0.1 mg/kg epinephrine (s.c). We then trained animals with this protocol in a 7T Bruker Biospec scanner to obtain concurrent functional images during learning. To facilitate the detectability for the learning-induced alteration in the BOLD response and functional connectivity, a within-subject paradigm was adopted by arranging the functional scans of CS-only, US-only, and CS/US pairing in sequence and interleaved with a 10-min-resting state scan. The BOLD response during CS-US association showed that the somatosensory and visual pathways had signals significantly enhanced as compared to the sensory stimulation only (corrected $p < .05$). Moreover, the ventroposterior nucleus of thalamus showed increased functional connectivity with the superior colliculus and amygdala ($p < .01$) after sedated rats receiving association training. Our results showed the conditioning paradigm elicits activity change mainly in the sensory processing pathways, and the increased functional connectivity among the sensory thalamic structures and the amygdala might reflect the reverberation of activity during the consolidation phase following initial acquisition.

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**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

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**Program#/Poster#:** 529.13/VV78

**Topic:** I.04. Physiological Methods

**Support:** NSF IGERT 1250104

**Title:** Targeted wireless neuromodulation using magnetoelectric thin films

**Authors: *A. WICKENS**[1], J. ROBINSON[2]
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**Abstract:** Chronic neuromodulation for treating neurological disorders and probing neural circuits is growing in popularity; however, testing new stimulation paradigms in animal models like rats and mice often requires lightweight, wireless neuromodulation technologies that can target specific brain areas. Many wireless stimulators designed for humans and NHPs are too large for experiments in mouse models due to the weight of batteries or receiver coils, requiring significant redesign. Here we present a new approach for wireless neuromodulation that uses a material to convert magnetic fields that freely penetrate the brain into an electric field that stimulates nearby neurons. Because these materials act as targeted wireless stimulators, they can be made small enough to be fully implanted in mice. To create these biocompatible "magnetoelectric" materials we fabricated a film of a piezoelectric material polyvinlydene fluoride bonded to a magnetostrictive film of Metglas. We then encapsulated the final films to make them biocompatible. These films can generate voltages above three volts under resonant conditions using alternating magnetic fields with an amplitude of about 1 mT. With these magnetoelectric films we demonstrate that a simple film is able to stimulate cellular activity *in vitro* in excitable HEK cells. Based on this proof of concept work, we fabricated magnetoelectric "micro-films" which weigh less than 5 mg and are compatible with studies in freely moving mice. Our results show that magnetoelectric materials offer great promise for wireless electrical stimulation of specific brain areas. The basic understanding of how this system operates could also be used to develop novel magnetoelectric materials or geometries (such as nanoparticles or nanofibers) to achieve even more targeted and less invasive wireless neural stimulation.

**Disclosures: A. Wickens:** None. **J. Robinson:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

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**Program#/Poster#:** 529.14/VV79

**Topic:** H.01. Animal Cognition and Behavior

**Support:** IUAP-P7/11

FWO-G.0007.12N

FWO-PDOH/13

H2020-HBP

**Title:** Effects of VTA electrical stimulation on whole-brain fMRI activity

**Authors: *S. R. MURRIS**, J. T. ARSENAULT, W. VANDUFFEL
Lab. for Neuro- and Psychophysiology, KU Leuven, Leuven, Belgium

**Abstract:** The Ventral Tegmental Area (VTA) is a small midbrain structure containing dopamine (DA) cells (+/- 60%) that project to a multitude of cortical and subcortical brain regions, with innervation patterns of macaque monkeys being more similar to humans compared to that of rodents [1]. Electrophysiology studies in the VTA indicated that DA neurons broadcast reward prediction error signals suggesting their role in reinforcement learning and motivational behaviour [2]. In support of this, cell type-specific optogenetic stimulation of VTA DA neurons in rodents has established a direct link between reinforcement learning and dopamine neuron signaling [3] [4]. The hypothesized functional roles of VTA dopamine are also supported by recent work in our lab in which electrical microstimulation of the VTA (VTA-EM) can alter choice preference when monkeys are performing a behavioural task [5], findings that are confirmed by a recent DA-specific optogenetic stimulation study [6]. Interestingly, we also showed that VTA-EM combined with fMRI demonstrates an increase in fMRI activity in brain regions commonly associated with reward, which are anatomically connected to the VTA, either directly or indirectly. Stimulation parameters in these experiments were based on cortical stimulation experiments, stimulating at 200 Hz for 200 ms with amplitudes ranging between 100-400 μA. Stimulation frequency, however, has previously been shown to greatly affect signal propagation as measured by the hemodynamic response with fMRI throughout the brain when stimulating thalamic nuclei such as the lateral geniculate nucleus (LGN) in macaques [7] and the ventral thalamus in swines [8]. In addition, endogenous firing patterns of VTA DA cells are highly variable operating at different timescales; which has been proposed to influence behavioural functions and brain wide activity differentially [9]. We investigated frequency-dependent effects of stimulation by applying VTA-EM with concurrent fMRI in two awake macaque monkeys (*Macaca mulatta*) (n=2), with previously implanted chronic electrodes. While the monkeys are performing a passive fixation task in the MR-scanner we stimulated their VTA with biphasic pulses for 200 ms at four different frequencies: 10, 20, 50 and 100 Hz. The order of the frequencies is pseudo-randomized as to minimize anticipation and summation effects of stimulation. We observed substantially different fMRI patterns in cortical and subcortical areas elicited by different frequencies of VTA-EM based on general linear model (GLM) and multivariate pattern analysis (MVPA) methods.

**Disclosures: S.R. Murris:** None. **J.T. Arsenault:** None. **W. Vanduffel:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

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**Program#/Poster#:** 529.15/VV80

**Topic:** I.04. Physiological Methods

**Support:** US FDA Critical Path

**Title:** Neuromodulation with microelectrodes: Elasticity of water window and implication for tissue damage

**Authors: *P. A. TAKMAKOV**, Y. WANG
CDRH\OSEL, US Food and Drug Admin., Silver Spring, MD

**Abstract:** Neuromodulation devices are undergoing a period of rapid development. The growth of bioelectronic medicine is particularly noticeable with substantial investments from government and private sector being allocated for development of new therapies based on neuromodulation of peripheral nervous system. While a number of innovative approaches based on an acoustic, optical and magnetic interface with neurons have been proposed, electrical neurostimulation with microelectrode arrays remains a key approach to modulation that requires high spatial resolution. One challenge associated with electrical charge injection is a danger of tissue damage that can occur at certain stimulation conditions. This undesirable side effect is particularly important for peripheral nerves, as animal studies point to the lower threshold for tissue damage compare to that in central nervous system. The mechanism of tissue damage is not well understood, but irreversible electrochemical reactions that occur during charge injection and lead to a generation of potentially toxic chemical compounds are thought to be a contributing factor. Water electrolysis is traditionally considered as one of these reactions that defined maximum potential excursions and maximum charge density that can be used safely during neuromodulation. However, quantification of this reaction during rapid current pulses used in neuromodulation has not been performed. In this work, we performed analysis and quantification of irreversible electrochemical reactions that occur during neuromodulation pulses at a rapid time scale (down to 100 us) on platinum electrodes of different diameters (from 10 to 1000 um). We observed that for microelectrodes, water electrolysis occur at much lower cathodic potential (-1.5 V vs Ag/AgCl for 10 um electrode) compare to macroelectrodes (-1.13 V vs Ag/AgCl for 1000 um electrode). This leads to much larger formal charge injection capacity (157 $mC/cm^2$ for 10 um vs 0.16 $mC/cm^2$ for 1000 um). This finding provides a new insight into the mechanism of tissue damage suggesting that electrical neurostimulation at a much large charge injection amplitudes can be performed without production of toxic electrochemical species. Additionally, this work provides a new method to measure charge injection capacity for rapid neuromodulation pulses.

**Disclosures: P.A. Takmakov:** None. **Y. Wang:** None.

**Poster**

**529. Methods: Physiology and Circuitry II**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 529.16/VV81

**Topic:** I.04. Physiological Methods

**Title:** OpenBehavior: Accelerating behavioral neuroscience through the promotion of collaboration and open science

**Authors: *M. W. PRESTON, JR**[1], *M. W. PRESTON, JR[1], H. C. GOLDBACH[2], S. R. WHITE[2], T. K. SWANSON[2], L. M. AMARANTE[2], A. V. KRAVITZ[3], M. LAUBACH[2]
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**Abstract:** Open science involves disclosing all methods (open methodology); releasing all raw and processed data (open data); and providing access to all software, as well as, documentation of all hardware utilized in an experiment (open source). Several resources exist within the neuroscience community for sharing this type of information, including OpenNeuroscience, Open Ephys, and OpenOptogenetic. OpenBehavior (http://edspace.american.edu/openbehavior/) was recently developed as a resource to specifically serve the behavioral neuroscience community. OpenBehavior is dedicated to accelerating behavioral neuroscience research through the promotion of collaboration and open-source projects. OpenBehavior aims to foster an international community of sharing by providing a centralized repository of open-source hardware (tools, devices, apparatuses), as well as software for the investigation of animal behavior and cognition. OpenBehavior accelerates behavioral neuroscience research through two principal means: (1) improvement of research methodology, and (2) reduction of research costs. OpenBehavior provides a platform for sharing devices and other resources for behavioral neuroscience research with research groups and educators seeking STEM neuroscience projects. This sort of sharing reduces duplication of effort between labs, as well as refines research methodology by allowing researchers to extend the work of others. Moreover, OpenBehavior dramatically reduces the cost of launching a behavioral research lab or extending existing research methods by providing a platform for sharing alternatives to commercial research equipment.

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**Poster**

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**Topic:** I.04. Physiological Methods

**Support:** Brazilian Ministry of Education (MEC)

Coordination for the Improvement of Higher Education Personnel (CAPES)

Santos Dumont Institute

**Title:** Electrode design and test for spinal cord stimulation

**Authors: L. R. C. CAVALCANTI**[1], H. S. PEREIRA[2], *E. MORYA[3]
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**Abstract:** An magnetic anchored electrode design is proposed here to electrically stimulate dorsal column fibers of the spinal cord in rats. One of the application of this electrode is to alleviate motor symptoms in Parkinson's disease under the assumption that that SCS might suppress the aberrant beta-frequency synchronous corticostriatal oscillations, thus restoring neural activity in the primary cortex and dorsolateral striatum to a state observed prior to the onset of spontaneous locomotion. Biocompatible materials were chosen to make a fully functional implantable device. Platinum (Pt) foil (99.9% purity) was used for rectangular electrical contacts measuring
1.0 x 0.8 mm (25 µm thick). Under exhausting repeated cycles of electrical stimulation, Pt foil suffers mechanical deformations on its surface. This can lead to significant electrode, impedance and biocompatibility changes. Thus, these electrodes should undergo electrical stimulation in order to shed light into a systematic therapy using SCS, such as Parkinson, and chronic pain. Electrodes underwent wettability and electrical impedance tests before and after 48 h of electrical stimulation in saline solution 0.9% at a frequency of 100 Hz, and 1.6 mA intensity. Wettablity test was performed to quantifying the hydrophilicity degree as a biocompatibility parameter. Both the silicone paddle and the platinum contacts have shown hydrophobicity before and after stimulation, as desired for implantation in soft tissue such as the spinal cord tissue. Electrical impedance test showed that electrochemical interactions did not cause lack of electrical behaviour consistence.

**Disclosures: L.R.C. Cavalcanti:** None. **H.S. Pereira:** None. **E. Morya:** None.

**Poster**

**530. Machine Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 530.01/VV83

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** NSF Grant 1144469

NIH Project 5U01NS090562-03

**Title:** Circuits in the retina: A deep learning framework for biological modeling and experimental design

**Authors: *D. BAGHERIAN**, T. KIM, Y. YUE, M. MEISTER
BBE, Caltech, Pasadena, CA

**Abstract:** Circuit neuroscience aims to describe the computations performed by groups of interconnected neurons in the way one might think of an electronic circuit board. Individual components connected in myriad different patterns can perform arbitrarily complicated transformations of an input signal. In light of the great complexity of the brain and given that its connectivity is at best partially known, a rigorous modeling paradigm is needed to generate a comprehensive list of circuit hypotheses that meet biological constraints and explain electrophysiological data.
We have developed a technique that employs a convolutional neural network (CNN) to fit the relationship between input and output of a neuronal circuit. By rigorously pruning away the synapses in its hidden layers, the network can infer the inner structure of the circuit. Unlike a typical machine learning application, the goal of this deep learning problem is to learn the structure of the neuronal circuit, not simply to predict its output. Success depends heavily on regularization by partial knowledge of the brain structure under study. We apply this technique to ON-OFF direction selective (DS) circuits in the retina, where we have a great deal of anatomical and physiological foreknowledge with which to constrain the CNN model, as well as direct access to the circuit input (visual stimuli) and output (retinal ganglion cell firing).
Given a limited predetermined set of standard stimuli, it is likely that many such CNN models will explain retinal responses equally well. Hand in hand with the development of this modeling paradigm, we aim to improve the efficiency of electrophysiological experiments by optimizing stimulus selection to quickly eliminate ambiguities in the CNN model structure. We investigate an algorithmic sequential experimental design paradigm in which a CNN model is adapted continuously during a retinal recording. At each training iteration, the next stimulus is selected based on uncertainty inherent to the current, partially-trained CNN. This active learning method reduces the experimental time necessary to resolve differences between hypothesized circuit models. The goals of rigorous model selection and adaptive experimental design complement each other in the pursuit of a better workflow for understanding neuronal circuits.

**Disclosures: D. Bagherian:** None. **T. Kim:** None. **Y. Yue:** None. **M. Meister:** None.

**Poster**

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**Topic:** I.06. Computation, Modeling, and Simulation

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**Title:** Multi-input deep learning models for brain computer interface headset transfer

**Authors: *A. SOLON**[1], S. M. GORDON[2]
[1]DCS Corp., Aberdeen proving ground, MD; [2]DCS Corp., Alexandria, VA

**Abstract:** As brain computer interfaces (BCIs) move toward ‘big data’ approaches, models must learn across different users, experiments, and potentially different electroencephalography (EEG) headsets. While user-to-user transfer learning (TL) is actively researched, TL’s use in cross-experiment and -headset learning remains relatively untouched, as does the use of deep learning (DL) methods for these BCI transfer problems. Building upon EEGNet, a user-independent DL-BCI model, we investigate the cross-headset problem and introduce a multi-input EEGNet variant which can learn across headsets that vary in both electrode number and layout. We validate our approach by improving the performance of a lower performing ‘target’ dataset (collected from one headset) by augmenting the learning process with a higher performing ‘source’ dataset (collected from a different headset). Our target dataset (N=109) was recorded using 64 channels (Physionet Motor Movement/Imagery dataset). When cued, subjects imagined right/left hand movement in 4s increments; we extract trials [1.0s, 3.0s] and [2.0s, 4.0s] post cue onset (45 trials per class, per subject). Our source dataset (N=9) was recorded using 22 channels (BCI Competition IV dataset 2a). We extract trials [0.5s, 2.5s] post cue onset for right/left hand motor imagery trials (144 trials per class, per subject). Each dataset was downsampled to 128Hz and bandpass filtered between 8- 30Hz to remove ocular artifacts. We generate 30 folds of the target dataset (15-40 training, 30 validation, and 15 test subjects). In addition to the available target training data, the multi-input headset transfer model is also trained on all available source data. This headset transfer model learns, per headset, a set of unique spatial filters in its first layer, but shares identical architecture and parameter updates for the remaining, higher level layers. We see a significant improvement (+.02 AUC, p < .05) compared to baseline performance at all target training set sizes, indicating that this novel approach can train a model on, and successfully transfer knowledge between, multiple unique headsets.

**Disclosures:** **A. Solon:** None. **S.M. Gordon:** None.

**Poster**

**530. Machine Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 530.03/VV85

**Topic:** I.06. Computation, Modeling, and Simulation

**Title:** Classification of neural cell types from extracellular signatures on multi-electrode arrays using deep learning

**Authors: *A. P. BUCCINO**[1,4], T. V. NESS[5], G. T. EINEVOLL[5], G. CAUWENBERGHS[4], T. HAFTING-FYHN[2], M. FYHN[3], P. HÄFLIGER[1]
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**Abstract:** The brain contains multiple neuron cell types which can be classified in different manners based on their morphology, electrophysiological characteristics, and gene expression. Extracellular recordings from large population of neurons in awake animals is widely used, but classification of neurons with this technique is limited to *putatively* excitatory or inhibitory units based the spike shape. Narrow waveforms are considered to be fast spiking inhibitory neurons and broad waveforms excitatory neurons. Thus, a lot of potential important information is not extracted from these large datasets. The aim of this work is to use the rich spatial information from high density Multi-Electrode Array (MEA) (e.g. from Schröder et al. 2015) to make such classification more robust and also be able to classify subtypes of excitatory and inhibitory neurons. To achieve this, we first built, in simulation, a large dataset of action potentials from detailed neural models (Markram et. al 2015) from a multitude of neuron cell types of various morphological and electrophysiological phenotypes (for example different pyramidal cells, basket cells, bitufted cells, double bouquet cells, bipolar cells). Then we extracted spike features from the simulated recordings on a 10x10 MEA model with inter-electrode-distance of 15 μm. Finally we used such features, as spike amplitudes and width, as input for a deep learning algorithm, namely Convolutional Neural Networks (CNN), to classify the different cell types. Compared with the *ground truth* data from the simulated dataset, the results show that this forward modelling/machine learning approach is very robust in recognizing excitatory and inhibitory spikes and to a certain extent, correctly classifies different cell subtypes. As the detail and fidelity of neural models increase, this approach could become a viable and robust alternative for classification of neural cell types from in-vivo extracellular recordings.

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**Poster**

**530. Machine Learning**

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**Program#/Poster#:** 530.04/VV86

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** GOIPG/2014/418

**Title:** When to use what algorithm: An empirical exploration of machine learning for prediction with neuroimaging data

**Authors: *L. JOLLANS**, R. WHELAN
Trinity Col. Inst. of Neurosci., Trinity Col. Dublin, Dublin, Ireland

**Abstract:** Background: With the increasing availability of large neuroimaging datasets, neuroimaging researchers have adopted machine learning analysis approaches developed for data science. However, there has been no empirical exploration of the strengths and limitations of most analysis tools that are already being used for neuroimaging research.
Method: Here we compared cross-validated linear regression accuracy of standard multiple regression (MR), regularized regression via the Elastic Net (EN), and random forest (RF). Analyses were carried out using simulated neuroimaging data. Sample sizes (N) varied between 75 and 2000, and number of input features (F) varied between 75 and 1000. We also evaluated if the addition of feature selection (FS) and bootstrap aggregation (bagging) improved accuracy.
Results:RF and EN outperformed MR, particularly when F≥N. There were no large differences between EN and RF. EN was less likely to outperform MR with small N, and RF slightly outperformed EN for N≤200. FS improved performance of MR for N=75 and large F, and bagging improved performance of MR when F>N. FS and bagging both improved performance of EN for N≤400, with no consistent additive effect of using both approaches simultaneously. FS reduced performance of RF. Bagging could not be implemented for RF.
Discussion:Machine learning is a substantial improvement over traditional methods such as MR and can produce reliable results even with high-dimensional neuroimaging data. EN and RF are both prefereable to traditional MR, and EN but not RF can be enhanced using additional machine learning techniques. Small datasets benefit more from these techniques, but combining multiple approaches is redundant. Due to the readability of models we recommend EN for use in neuroimaging models.

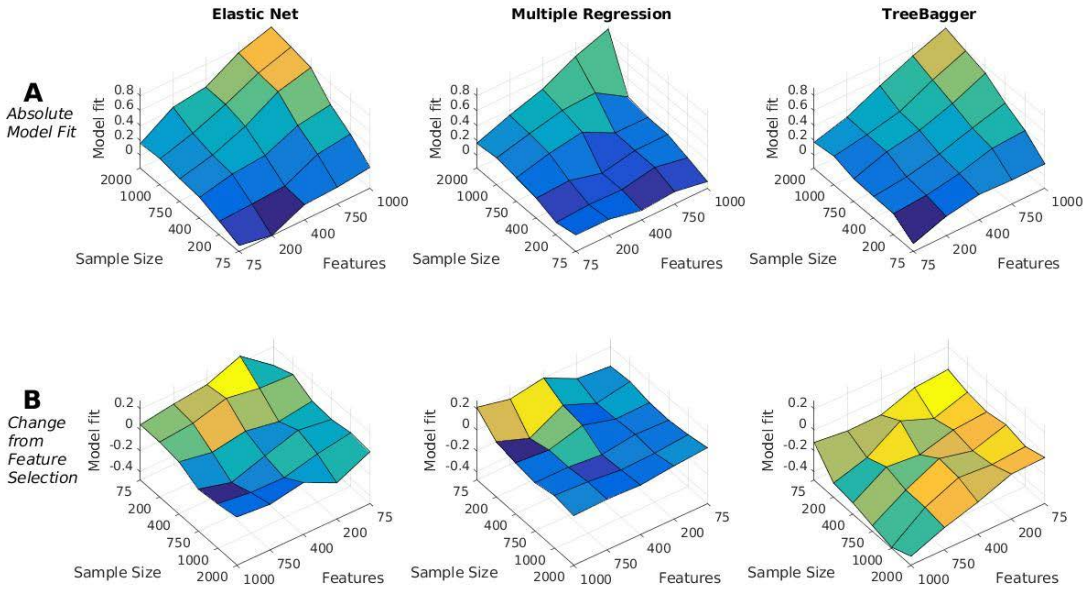

*Figure 1. Model fit across sample sizes and number of input variables for the Elastic Net, standard multiple Regression, and random forest. Model fit is the correlation between predicted and actual values. A: Absolute model fit for EN, MR, and RF. B: Change in model fit from adding Feature selection to each approach.*

**Disclosures: L. Jollans:** None. **R. Whelan:** None.

**Poster**

**530. Machine Learning**

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**Title:** Using machine learning for automated animal call detection and classification

**Authors: S. SHARMA**[1], R. LANDMAN[5,6], K. SRINIVASAN[1], R. T. CHEUNG[2], *J. SHARMA[7], M. SUR[3], G. FENG[4], R. DESIMONE[8]
[1]McGovern Inst. for Brain Res., [3]Picower Inst. for Learning and Memory & Simons Ctr. for Social Brain, [4]Brain and Cognitive Sci., [2]MIT, Cambridge, MA; [5]MIT, [6]Broad Inst., Cambridge, MA; [7]Picower Inst. For Learning & Memory, MIT and MGH, Cambridge, MA; [8]MIT, McGovern Inst. Brain Res., Cambridge, MA

**Abstract:** In order to use behavioral observations of freely moving animals for neuroscience research, objective measurement and quantification is essential. In the context of vocalization studies involving the common marmoset monkey (Callithrix Jacchus), data processing tends to take the form of analyzing hundreds of hours of audio recordings. Processing this data manually has several drawbacks, such as being slow, labor-intensive, imprecise, and subjective. We present a software framework for automated Animal Call Detection and Classification (ACDC), designed for researchers to be able to easily train and utilize models to turn hours of recordings into structured data that specifies the type and time-stamp of each animal vocalization. There are two main tasks that this software performs: detection, and classification. The detection task involves determining which segments of the audio include relevant animal vocalizations, while

rejecting environmental noise, audio artifacts, human voices etc. The classification task involves taking these extracted audio segments and categorizing them into the types of vocalizations the software has been trained to detect. In order to train ACDC, a “call dictionary” of audio samples of each type of vocalization, as well as samples of noise, is provided. The detection approach then utilizes traditional audio feature extraction techniques in combination with a neural-network-based model to learn from these samples and provide a set of timestamps specifying where vocalizations were detected. The classification approach, in turn, mimics how a human might classify these distinct sounds. Since different types of vocalizations tend to have a unique, easily recognizable shape to their spectrogram, we treat this as an optical character recognition problem. We converted spectrograms into images and trained a convolutional neural network to perform classification on the resulting shapes. We used ACDC to analyze audio from small groups of marmosets, training the models to detect the five or so most common types of vocalizations. Our initial results are promising, reaching > 80% accuracy on the detection task and better than 90% accuracy on the classification task. Our priority for further work is to continue to improve accuracy, while keeping the code clean, modular, and adaptable for use by other researchers, with a view to open sourcing in the future.

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**Poster**

**530. Machine Learning**

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**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** NSF1738286

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**Title:** Learning multi-layer and feedback network structures in mu-ECoG data

**Authors: M. SAHRAEE-ARDAKAN**[1], *A. FLETCHER[1], M. TRUMPIS[2], B. BENT[2], J. VIVENTI[2]
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**Abstract:** Micro-electrocorticography (mu-ECoG) now offers the possibility of recording brain activity over large cortical regions at high spatial and temporal resolutions. However, using these recordings to develop accurate functional models of neural circuits and their responses to stimuli remains challenging. The underlying neural systems are composed of tremendous numbers of

functional units with complex, nonlinear dynamics and interactions. This abstract proposes a novel approach for identification of complex dynamical network models from high-dimensional time series data that is particularly well suited for neural modeling. The key concept is to decompose large-scale systems into networks of low-dimensional linear dynamical subsystems, with memoryless, scalar nonlinear feedback elements, and memoryless, linear interactions. The model, which we call Dynamic Neural Networks (DyNNets), readily applies to a wide range of meso-scale models of neural processes including neural mass models and multi-layer models with or without feedback. We show that the decomposition structure of the proposed DyNNet model greatly reduces the computational challenges in learning large-scale systems. In particular, the posterior density of the hidden states given the unknown parameters of a DyNNet admits a factorable structure that separates the linear dynamics, memoryless nonlinearities, and linear interactions. This factorization enables efficient implementation of MAP state estimation and system identification via the alternating direction method of multipliers (ADMM). The methods are illustrated in learning multi-layer models of the rat primary auditory cortex (A1) using a high-resolution flexible electrode array. The array has 61 electrodes with 400 mu-m spacing. Importantly, these arrays are both flexible and non-penetrating, enabling the arrays to be scaled up to record and stimulate larger areas of the cortex without damage, allowing observations in the changes in the model over durations of months to years.

**Disclosures: M. Sahraee-Ardakan:** None. **A. Fletcher:** None. **M. Trumpis:** None. **B. Bent:** None. **J. Viventi:** None.

**Poster**

**530. Machine Learning**

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**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** GAANN Grant

**Title:** Deep dynamic programming: Learning state-action space on-line to rapidly generate optimal controllers

**Authors: *A. LONSBERRY**, A. LONSBERRY, R. QUINN
Case Western Reserve Univ., Cleveland, OH

**Abstract:** Current model-free learning (machine-learning) systems rely on observable state/action pairs recorded in memory for decision making. In most scenarios, memory of the environment, state, and actions is saved for a fixed number of time-steps. The cost-to-go for the remembered states is only updated if the current state has a reward value associated with it. Systems of this type may not be able to well optimize a controller over a large state-space given

the necessity for large memory and the need to visit much of the state-space. Generally, these approaches are time intensive, especially if the state and action spaces are continuous. To alleviate these issues, we deploy a more biologically inspired system of disjoint deep neural networks that learn and are able to generalize about the environment on-line. The learned knowledge about the environment is then leveraged to more quickly generate a control policy. We present a new method for model-free continuous update control, called Deep Dynamic Programming (DDP), which expands upon the Q-learning structure and dynamic programming. Q-learning only updates the cost-to-go function once a reward state is found and only based on the most recent set of states visited and stored in memory. DDP expands on Q-learning by *also* generating updates to the cost-to-go function for other state-space regions not recently visited by an agent. As an agent explores state-space, it simultaneously learns about itself and the environment. This knowledge of state-action space is encapsulated in a set of neural networks, where each network is responsible for a limited part of the entire state-space. This learned model of state-action space provides the ability to update the cost-to-go function on state spaces that have not been observed or have not been observed recently enough. That is, using the learned model of state-action space, we perform local updates to the cost-to-go using backwards induction. This inclusion of environmental modeling and generalization about the cost-to-go locally provides for rapid generation of control policies.To demonstrate the applicability of this technique, a controller was developed for an underactuated double inverted pendulum moving on a cart. The system was able to learn how to swing both pendulums into the upright position and keep them stabilized against disturbances.

**Disclosures:** **A. Lonsberry:** None. **A. Lonsberry:** None. **R. Quinn:** None.

**Poster**

**530. Machine Learning**

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**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** DC014701

DC014367

**Title:** Transfer learning model of sensory inputs in the external plexiform layer network of olfactory bulb

**Authors: *A. BORTHAKUR**, T. A. CLELAND
Psychology, Cornell Univ., Ithaca, NY

**Abstract:** Recurrent interactions between mitral and granule cells in the external plexiform layer (EPL) of the mammalian olfactory bulb (OB) transform primary odor representations before relaying them to targets such as piriform cortex. Specifically, EPL lateral inhibition appears to both decorrelate overlapping primary odor representations and transform their underlying coding metric into a dynamically regulated spike timing-sensitive form. We sought to determine experimentally supportable rules for activity-dependent plasticity in the EPL that enable pattern separation among highly-overlapping odor representations, including γ/β-band dynamics and the phase-constrained spiking of mitral cells. We began by assessing the effect of timing-dependent learning rules at EPL recurrent synapses. We show that an asymmetric spike timing-dependent plasticity (STDP) rule in the excitatory (mitral-to-granule) synapses of this network can generate higher order receptive fields(HORF) in granule cells, enabling them to learn patterns of covariance derived from the external environment. In addition, an asymmetric inhibitory STDP rule in the granule-to-mitral cell synapses trains the network to competitively inhibit weakly activated MCs in an odor-specific manner. The weight matrices produced by these learning rules greatly improve the capacity for the multi-class classification of odor stimuli, including their statistically determined generalization gradients, and reduce or eliminate the cross-contamination of plasticity among odorants with overlapping primary receptor activation profiles. Moreover, as this algorithm necessarily consumes granule cells via irreversible differentiation, our simulations indicate that a supply of new, undifferentiated neurons via adult neurogenesis is required for the sustainable operation of odor learning in this network. We therefore offer a theory of the utility of OB adult neurogenesis. Finally, we propose that these irreversibly differentiated GCs serve as informative priors for future odor encounters (transfer learning), facilitating the detection and identification of odors of interest within unpredictable, high-noise environments.

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**Poster**

**530. Machine Learning**

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**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** CREST , Japan Science and Technology Agency

**Title:** A local supervised learning rule protects memories from catastrophic interference during subsequent unsupervised learning

**Authors: *A. J. DECOSTANZO**[1], T. FUKAI[2]
[1]RIKEN, Wakoshi, Japan; [2]Brain Sci. Inst., RIKEN, Wako, Japan

**Abstract:** While human memory is remarkably persistent in the face of new learning, artificial neural networks suffer from 'catastrophic interference', the rapid forgetting of prior memories upon acquisition of new ones. Furthermore, much of human learning occurs without supervision - that is, without a label for every example of some category. Yet it is difficult to achieve such 'unsupervised learning' in artificial networks in a way that clearly improves their performance. These two difficulties suggest that human memory may be encoded with learning rules other than those currently employed in training artificial neural networks. Though these problems may seem distinct, we present a learning rule that reveals a close relationship between successful unsupervised learning (that which improves accuracy on hold-out test examples) and the avoidance of catastrophic interference.

**Disclosures: A.J. DeCostanzo:** None. **T. Fukai:** None.

**Poster**

**530. Machine Learning**

**Location:** Halls A-C

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**Program#/Poster#:** 530.10/VV92

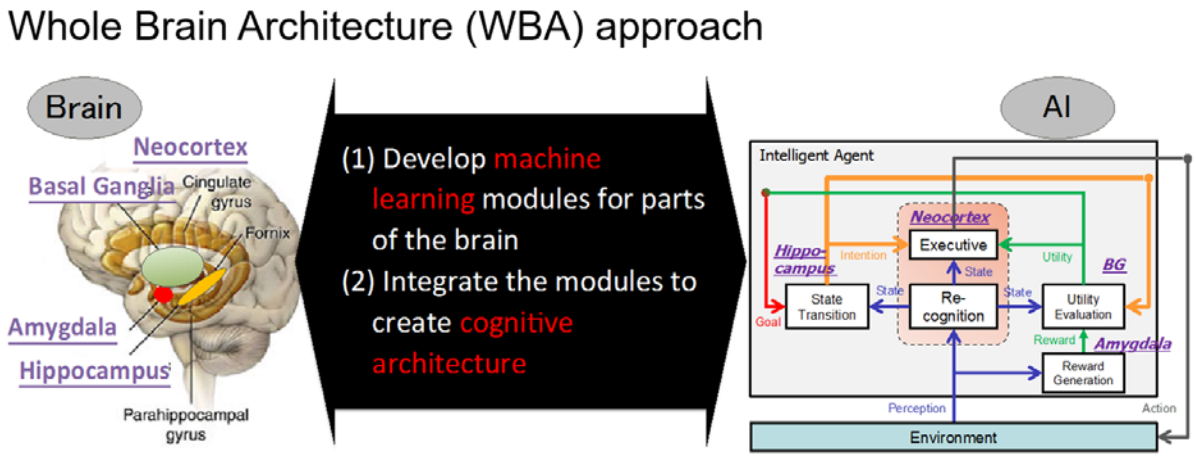
**Topic:** I.06. Computation, Modeling, and Simulation

**Title:** Whole brain architecture for open development of general artificial intelligence based on connectomes

**Authors: *H. MIZUTANI**[1], *H. MIZUTANI[1,2], M. UENO[1,2], N. ARAKAWA[1,2], H. YAMAKAWA[1,2]
[1]Artificial Intelligence Lab., Dwango, Tokyo, Japan; [2]Whole Brain Architecture Initiative, Tokyo, Japan

**Abstract:** Whole Brain Architecture (WBA) is considered to be a good candidate for the cognitive architecture of an artificial general intelligence (AGI) computing platform which consists of empirical neural circuit information in the entire brain. It is constructed with the aim of developing a general-purpose biologically plausible AI to exert brain-like multiple cognitive functions and behaviors in a computational system. The goal of our brain-inspired AGI is to develop a software program that can learn and adapt to the environment similar to the way humans do. It will provide innovative solutions in a variety of fields without deploying problem-specific algorithms. We have created a neuroscientific design of the reference architecture called Whole Brain Connectomic Architecture (WBCA) built by utilizing experimental connectomic data acquired from three-dimensional microscopic brain imaging techniques. It includes static information on wiring diagrams of the brain neural circuits with directed graphs to determine neural network flows. We have developed particular functional machine learning modules corresponding to specific brain regions along with the connectomic information, including parts of the cerebral cortex, thalamus, hippocampus and basal ganglia. Those computational modules

we developed are designed at the mesoscopic level neural connectivity, and the individual modules are connected based on the topology of the neural circuits in the brain. We have developed and implemented several functional machine learning modules in collaboration with neuroscientists and developers. Therefore, WBA can help accelerate the development of AGI algorithms on the open platform which has been based on the biological neural circuits.




**Disclosures:** **H. Mizutani:** None. **M. Ueno:** None. **N. Arakawa:** None. **H. Yamakawa:** None.

**Poster**

**530. Machine Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 530.11/WW1

**Topic:** I.06. Computation, Modeling, and Simulation

**Title:** Application of game theory and optimization techniques to intelligent decision making

**Authors:** ***H. C. YUAN**[1], M. CHAO[2]
[1]Independent Lab., San Marino, CA; [2]Independent Lab., Rancho Palos Verdes, CA

**Abstract:** Past studies in neurobiology have used game theory to explore how behavior may require decision making strategies (Alan Sanfrey, “Social Decision-Making: Insights from Game Theory and Neuroscience”, Science Oct 2007). This poster examines how game theory can be applied to a model of human decision making. Game theory is a branch of mathematics that deals with the analysis of games or situations involving parties with conflicting interests and strategies. Game theory can provide an objective, computational tool to intelligently decide and manage these strategies. The principles of game theory has many applications to real-world

problems as diverse as economics, politics, and avionics. Classical game theory features both hidden information and chance elements which contribute to the intelligent decision process. The intelligent selection of strategies in a game usually strives to achieve an objective that is either maximized or minimized, or even a saddle point. The selection of various strategies among opposing players or teams could be considered as a zero-sum game. The level of success of a selected strategy means the equal level of failure of the corresponding strategy in a zero-sum game framework. Together with game theory, linear programming is a method that could be employed to compute the best allocation of strategies to competing activities when expressed as a game aimed to achieving a linear objective function with linear inequality constraints. A linear program is setup with variables, a linear objective function indicating the contribution of each variable to the desired outcome, and a set of linear constraints describing the limits of the variables. The "answer" to a linear program is a set of values for the problem variables that results in the best, largest or smallest, value of the objective function and is consistent with all the constraints. This poster investigates how intelligent decisions can be considered as deciding among strategies to achieve an objective. An application to airborne avionics for radar sensor management and strategy management in surveillance, reconnaissance missions, and combat defense strategies is also given. This poster further examines the use of game theory in an avionics and sensor resource example with a 2-player zero-sum framework for intelligent selection of strategies, and the use of linear programming to compute best allocation of resources and strategies.

**Disclosures: H.C. Yuan:** None. **M. Chao:** None.

**Poster**

**530. Machine Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 530.12/WW2

**Topic:** I.06. Computation, Modeling, and Simulation

**Title:** A dynamic perceptron model

**Authors: *N. GRAYSON**, G. SILVA, V. GEORGE, F. PUPPO
Electrical Engin., UCSD, La Jolla, CA

**Abstract:** Since their conception, Neural Networks have been built of decision making nodes. Hopfield Networks, for example, have used perceptrons which function as simplified models of Neurons. Networks of these perceptrons have a storied history of success in recent years and have, in part, redefined Machine Learning and Artificial Intelligence as fields. We present and construct a dynamic model of a perceptron by extending the existing model to include the additional parameters of signaling delay, refractory period, and dendritic decay.Signaling delay is a simplification of the travel speed and the physical path between neurons. Refractory period is

a time after which a node activates that it can not activate and it ignores input stimulus. When a node is non-refractory and therefore able to receive signals, these signals each contribute to the node's activation energy. Unlike classical perceptrons which sum inputs at each time step, these dynamic perceptrons have a 'memory' of received signals. Signals received further in the past contribute less to activation threshold than recently received signals. This lessened contribution is modeled through a dendritic decay function.The addition of parameters to the classic model of a perceptron naturally leads to an increased number of possible states (refractory, halfway to activation, etc). As such, in (ref), we prove that this dynamic model of a perceptron is able to encode more information. By extending the architectures of Hopfield Networks, Liquid State Machines, and other recurrent networks into the time domain and using our dynamic model of a perceptron, we create trainable dynamic networks.

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**530. Machine Learning**

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**Topic:** I.06. Computation, Modeling, and Simulation

**Title:** Drowning in Data: Using predictive analytics to advance outcome measures in neurosciences research settings

**Authors: *A. L. ORTIZ-VELEZ**[1,2], A. MARCUZ[3]
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**Abstract:** Preamble
Data, the most used word in research today, but, are we making the best of what we collect? Are we using it effectively to advance the field of neuroscience?
It is the intent of this researcher presentation to stir the mind of neuroscientists on how to expand and advance the neuroscience field by partnership with Data and Computer Science professional(s) to catapult neuroscience to the future of outcome measures. The neuroscientist, choose the data of interest, the computer scientist implement this method of analyzing the collected data samples.
Using regression and predictive analytics models, we can generate predictive outcomes. The method described here does not require expensive and sophisticated proprietary software applications, but it requires partnering of two different but alike disciplines Neuro Medical professional and Computer Science Data Analyst who creates the analytical "engine" for

processing the data.

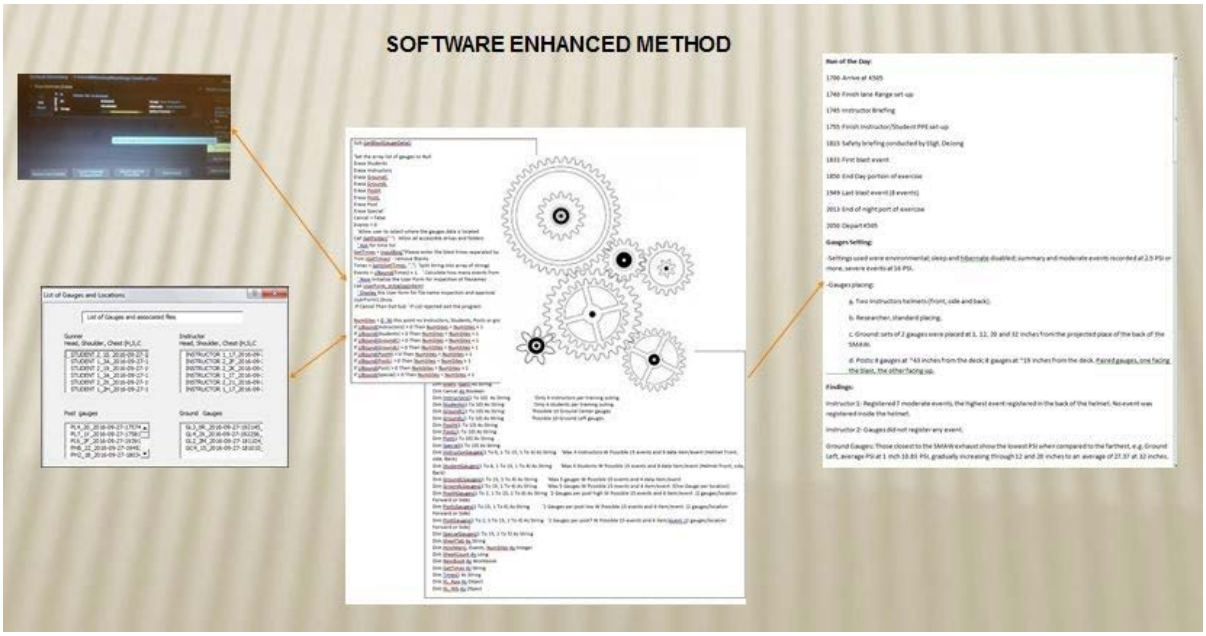
Method

By using the underlying software interface available on most computers (which is used to generate documents or spreadsheets whether proprietary or Open source) the computer science professional collects the data samples that the Neuroscience professional(s) have recorded. The Computer Science professional creates an analytical engine method which will analyze the intake and outcome data, perform regression analysis, generating statistical modeling. By further associating the statistical analysis with outcome creates a predictive model of outcome.

This method model can be further tuned or re-adjusted after the predictive analysis is performed. The analysis is restarted and quickly the output can be reviewed and evaluated by Neuroscience professionals.

Conclusion

By levering the method and collaborative spirit described in this abstract, neuroscience professionals can greatly advance positive neuroscience clinical outcomes, increase patient wellness and improve data reliability.




**Disclosures:** **A.L. Ortiz-Velez:** None. **A. Marcuz:** None.

**Poster**

**530. Machine Learning**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 530.14/WW4

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** Chinese Academy of Sciences

**Title:** Robust reservoir computing achieved by self-organized criticality

**Authors: G. ZENG**, X. HUANG, T. JIANG, *S. YU
Brainnetome Ctr., Inst. of Automation, Chinese Acad. of Sci., Beijing, China

**Abstract:** It has been suggested that, through short term synaptic plasticity, neuronal dynamics in the brain are self-organized close to a critical state, which brings various functional advantages in terms of information processing to the system. Inspired by such an idea, here we investigate if and how self-organized criticality (SOC) can improve the performance of a recurrent artificial neural network (RNN) in information processing. To this end, we implemented short term synaptic depression into RNNs in different models of reservoir computing (RC) and tested its effects on sequence memory as well as pattern recognition tasks. We found that a simple form of plasticity greatly expanded the parameters range within which the RC models can perform well. In addition, it makes the system more robust to input noises. These results are achieved through dynamically maintaining the reservoir close to a critical state. Our study suggests that the SOC framework can be instrumental in optimizing the design of RNNs. In addition, these results shed new light on the functional benefits of short term synaptic plasticity for neural networks.

**Disclosures: G. Zeng:** None. **X. Huang:** None. **T. Jiang:** None. **S. Yu:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.01/WW5

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** Kavli Neuroscience Discovery Institute

Extreme Science and Engineering Discovery Environment

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**Title:** Tools for registering 11T ex-vivo MRI of the human medial temporal lobe to a standard atlas coordinate system

**Authors: *D. J. TWARD**[1], T. BROWN[2], B. LEE[1], J. T. RATNANATHER[2], S. MORI[3], J. C. TRONCOSO[4], M. MILLER[1]
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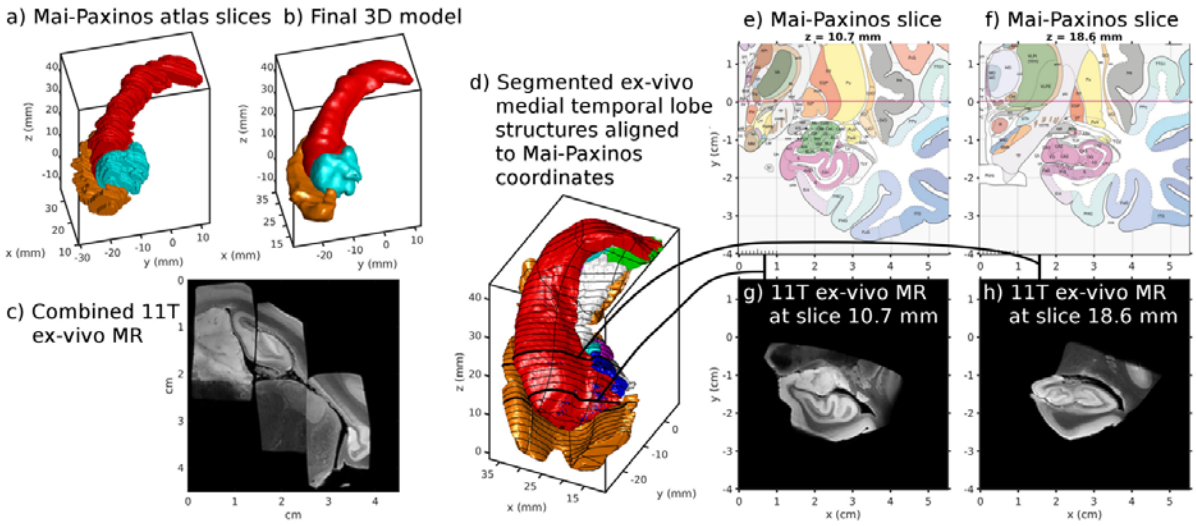
**Abstract:** The structures of the medial temporal lobe, such as the amygdala, hippocampus, entorhinal cortex and transentorhinal cortex, constitute the locus of some of the earliest anatomical changes in Alzheimer's disease. Because definitive diagnosis of this disease is made by examining neuropathology at autopsy, establishing reliable clinical neuroimaging biomarkers of the disease is difficult. Our work begins addressing the challenge of uniting clinical imaging and autopsy findings by developing computational tools for registering high field strength MRI of ex-vivo specimens to a standard coordinate system.
We chose the Mai-Paxinos atlas as such a standard, as it is commonly used by pathologists, radiologists, as well as neuroscientists. A surface model of the hippocampus, amygdala, and entorhinal cortex was constructed by first manually segmenting each slice; second rigidly aligning slices to remove small displacements and rotations; and third nonlinearly interpolating between slices by constructing a flow of deforming images to match neighboring slices using large deformation diffeomorphic metric mapping, and sampling the flow at arbitrary locations between them (Fig. 1a-b).
A medial temporal lobe was cut into 3 blocks for magnetic resonance imaging in the small bore of an 11T scanner. The B0 images of each block were rigidly aligned to reconstitute the medial temporal lobe (Fig. 1c), and structures of interest were manually segmented. Surface models were generated and aligned rigidly to the Mai-Paxinos surfaces (Fig. 1d). This transformation was applied to the aligned ex-vivo images (Fig. 1g-h), allowing visualization in standard coordinate system (Fig. 1e-f).
This framework will be used for ex-vivo imaging of up 20 to brains over the next two years, and will be expanded to place Nissl, amyloid, and tau histology of the ex-vivo specimens in the same coordinate system. These tools will be important for demonstrating a direct link between clinical neuroimaging biomarkers and autopsy findings.



**Disclosures:** **D.J. Tward:** None. **T. Brown:** None. **B. Lee:** None. **J.T. Ratnanather:** None. **S. Mori:** None. **J.C. Troncoso:** None. **M. Miller:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.02/WW6

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** Dana Foundation

GE Healthcare

DARPA (Cooperative Agreement Number W911NF-14-2-0013)

HHMI

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NIH Grant R01-MH111444

NIH Grant P41-EB015891

**Title:** Application of a novel CLARITY-MRI pipeline to mPFC projections improves connectivity mapping

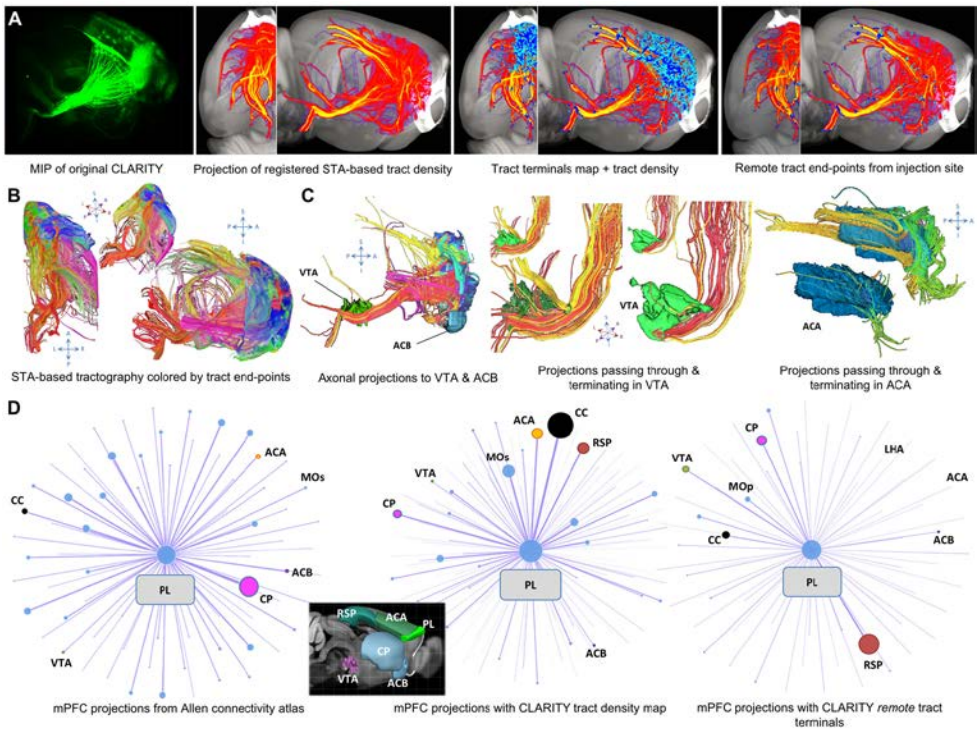
**Authors:** ***M. GOUBRAN**, C. LEUZE, B. HSUEH, M. ASWENDT, L. YE, Q. TIAN, M. CHENG, A. CROW, G. STEINBERG, J. MCNAB, K. DEISSEROTH, M. ZEINEH
Stanford Univ., Stanford, CA

**Abstract:** **Background**:
Neural networks are altered in many disorders, with implications on the affected region and connected areas. Connectivity atlases based on 2D serial sections are exceedingly valuable resources. However, they do not allow for 3D tractography and terminal zones computation, i.e. distinguishing passing fibers from endpoints (representing synapses). We present an automated resource that allows the assessment of wiring by comparing viral tracing with atlases, and investigation of circuitry based on CLARITY projection terminals.
**Methods:**
We developed a novel pipeline for the connectivity analysis of CLARITY, imaging and mouse atlases. We applied our pipeline to focal stereotactic injections of adeno-associated virus expressing fluorescence protein in the mPFC, to study efferent axonal projections. These

projections were quantified using structure tensors analysis (STA) from the CLARITY images. Terminal maps were automatically generated by computing the number of STA-based streamlines ending in a voxel after tractography, as implemented in *MRtrix3* (**Fig. 1a**). The number of terminating streamlines was then summed per registered atlas label.

**Results and Discussion:**

While connectivity based on tract density (passing fibers) suggested a stronger connection between mPFC and anterior cingulate area (ACA) than ventral tegmental area (VTA), terminal maps revealed a higher number of fibers terminating in the VTA (5.32x) (**Fig. 1c, d**). Similarly, caudoputamen (CP) is shown as a major node based on tracer signal while it is demonstrated to be less prominent based on terminating axons (283k passing vs. 121k terminating) (**Fig. 1d**). To validate our CLARITY streamlines we compared our tract density-based network graph with the graph representing projection density from the prelimbic area (PL) of the Allen connectivity atlas (**Fig. 1d**). A high overlap of 74 % was found between the two experiments. These results are in good accordance with literature of the reward network, which highlights the importance of connectivity based on terminals and its implications on connectome analysis.




**Disclosures:** **M. Goubran:** None. **C. Leuze:** None. **B. Hsueh:** None. **M. Aswendt:** None. **L. Ye:** None. **Q. Tian:** None. **M. Cheng:** None. **A. Crow:** None. **G. Steinberg:** None. **J. McNab:** None. **K. Deisseroth:** None. **M. Zeineh:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.03/WW7

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** ERC Grant ERC-2015-STG-677697

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Basque Govenment (Dpt. Educacion, politica linguistica y cultura) Grant PI2016-12

**Title:** A probabilistic atlas of the human thalamus based on *Ex vivo* MRI and histology

**Authors: J. E. IGLESIAS**[1], R. INSAUSTI[2], G. LERMA-USABIAGA[3], G. ARTACHO-TRILLOFIGUEROA[2], K. VAN LEEMPUT[4,5], S. OURSELIN[1], B. FISCHL[4,6], C. CABALLERO-GAUDES[3], *P. M. PAZ-ALONSO[3]
[1]Univ. Col. London, London, United Kingdom; [2]Univ. of Castilla La Mancha, Albacete, Spain; [3]Basque Ctr. On Cognition, Brain and Language, Donostia-San Sebastian, Spain; [4]Martinos Ctr. for Biomed. Imaging (Massachusetts Gen. Hospital), Charlestown, MA; [5]Dept. of Applied Mathematics and Computer Sci., Tech. Univ. of Denmark, Lyngby, Denmark; [6]MIT, Cambridge, MA

**Abstract:** The human thalamus is subdivided into several nuclei with concrete functions and connectivity. Segmentation of these nuclei can enable neuroimaging studies with higher specificity, compared with analyzing the whole thalamus. Previous work on automatic segmentation of thalamic nuclei relied on clustering diffusion MRI data, supervised classifiers, and non-probabilistic segmentations derived from delineations on histological samples. Here we present a probabilistic atlas of 33 thalamic nuclei and surrounding tissue built from MRI and histology data. Compared to previous work our atlas has the advantages of being probabilistic, modeling surrounding anatomy, and that it can be used in a Bayesian inference framework to segment MRI scans of arbitrary contrast, even if multimodal. Six formalin-fixed human brains were first scanned with a 3T scanner (multi-slab balanced SSFP, 0.25 mm isotropic). Coronal slices (~10 mm thick) were cut, and blocks containing the thalamus were further dissected,

cryoprotected and sectioned at 50-μm thickness, while taking block-face photographs. Every 10th slice was mounted, Nissl stained (thionin), and digitized at 4-μm resolution. An expert neuroanatomist (RI) traced 33 thalamic nuclei on the scanned images. The block-face images were perspective corrected, stacked and rigidly registered to the MRI. MR images were then resampled to the plane corresponding to each histological slice, and nonlinearly aligned the 2D image pairs. The concatenation of the rigid and nonlinear transforms provided a mapping between histology and ex vivo MRI, which was used to warp the manual delineations to MRI space and recover their 3D structure. The gaps between blocks were filled by combining a Gaussian mixture model with a Markov random field. Finally, the atlas was built merging the "filled" segmentations with manual delineations of 36 structures in 39 *in vivo* T1 scans. The atlas was encoded in an adaptive tetrahedral mesh endowed with a deformation model that effectively preserves its topology. A Bayesian segmentation algorithm was also implemented that combines the atlas with a likelihood term and is adaptive to MRI contrast. Using the probabilistic atlas, our segmentation method produces volume estimates of individual thalamic nuclei as well as masks that can be used as seeds for tractography or fMRI analysis. Future work will adapt the likelihood term so that the algorithm can handle diffusion MRI data and evaluate the performance of the segmentation with large datasets. The atlas and companion segmentation algorithms will be made publicly available as part of FreeSurfer.

**Disclosures:** **J.E. Iglesias:** None. **R. Insausti:** None. **G. Lerma-Usabiaga:** None. **G. Artacho-TrilloFigueroa:** None. **K. Van Leemput:** None. **S. Ourselin:** None. **B. Fischl:** None. **C. Caballero-Gaudes:** None. **P.M. Paz-Alonso:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.04/DP14/WW8 (Dynamic Poster)

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** RO1 EY019743

RO1 EY026812

U01 NS099702

IOS 1355075

EAGER 1649923

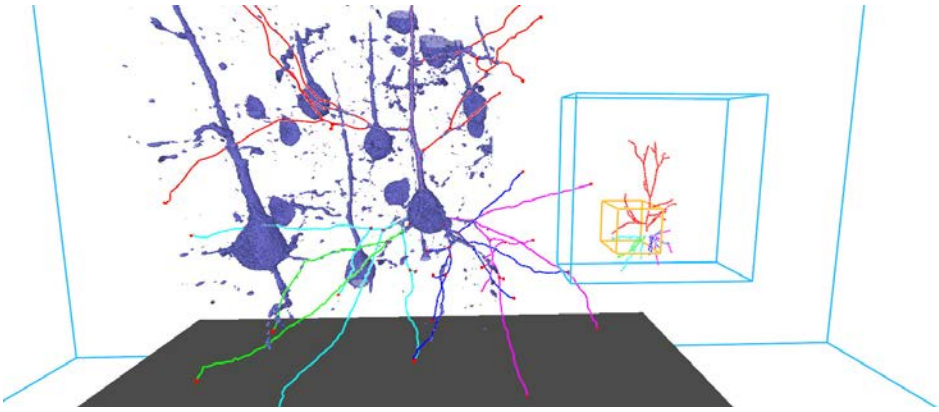
U of Utah seed grant 10040877

Research to Prevent Blindness

**Title:** A virtual reality visualization tool for neuron tracing

**Authors: W. USHER**[1], P. KLACANSKY[1], *F. FEDERER[2], P.-T. BREMER[1], A. KNOLL[1], A. ANGELUCCI[2], P. VALERIO[1]
[1]Scientific Computing and Imaging Inst., [2]Moran Eye Inst., Univ. of Utah, Salt Lake City, UT

**Abstract:** Tracing neurons in microscopy data is necessary to create circuit diagrams of the brain. Automatic techniques often fail for large and complex datasets (Peng et al. 2011) and connectomics researchers may spend weeks or months manually tracing neurons using 2D image stacks (Ascoli 2008). Here we present a new virtual reality (VR) system to trace neurons rendered in 3D from microscopy acquired image stacks. We hypothesized that using consumer-grade VR technology to navigate and trace neurons directly in 3D would increase the speed and ease of resolving complex cases and cause less physical and mental strain for the user. To test this hypothesis, we compared tracing accuracy and speed in VR versus the 2D desktop-based tracing tool Neurolucida. We explored different rendering, interaction, and navigation methods in VR, as well as the use of force feedback to improve the quality and speed of neuron tracing. Our VR tool also provides a scalable and flexible paging system built on the IDX file format (Pascucci and Frank 2001) to allow for interactive exploration and tracing of terabyte-sized datasets. The included figure shows a user's view in our tool (background changed to white to improve contrast).
In a set of trials we asked 4 experienced users of Neurolucida software to trace a series of publicly available fluorescently labeled neuron image stacks (DIADEM challenge, Neocortical Layer 1 Axons dataset) in both VR and on a desktop using Neurolucida. For each trial we measured the time it took users to complete the tracing as well as their tracing accuracy compared to the DIADEM reference tracings. We found that overall, there was no statistically significant difference between accuracy scores in VR vs. Neurolucida ($p=0.097$), however VR allowed for faster tracing. Specifically, in cases where subjects produced equivalent quality tracings in both tools, there was a statistically significant speedup in VR, with users being on average 1.7x faster in VR than in Neurolucida ($p=0.005$). We conclude that 3D VR tracing presents a promising alternative to current 2D desktop-based tracing approaches.



**Disclosures: W. Usher:** None. **P. Klacansky:** None. **F. Federer:** None. **P. Bremer:** None. **A. Knoll:** None. **A. Angelucci:** None. **P. Valerio:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.05/WW9

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** RO1 EY019743

RO1 EY026812

U01 NS099702

IOS 1355075

EAGER 1649923

U of Utah seed grant 10040877

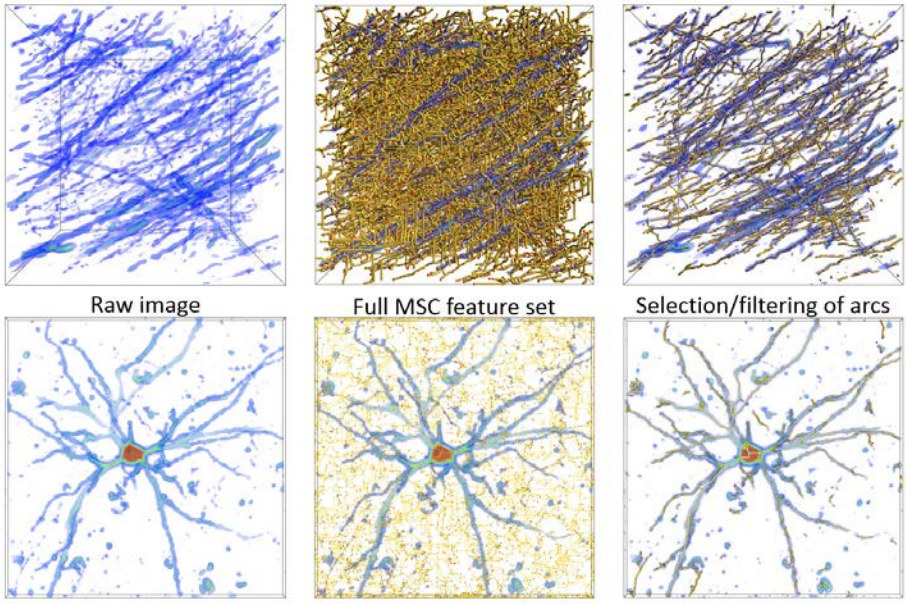
Research to Prevent Blindness

**Title:** A computational framework for automated neuron tracing using scalar field topology

**Authors: A. GYULASSY**[1], F. FEDERER[2], A. VENKAT[1], V. PASCUCCI[1], *A. ANGELUCCI[2]
[1]Scientific Computing and Imaging Inst., [2]Ophthalmol, Moran Eye Inst., Univ. of Utah, Salt Lake Cty, UT

**Abstract:** Obtaining a wiring diagram of the brain is crucial to understand brain function and dysfunction at a mechanistic level. As techniques improve, it is becoming increasingly feasible to obtain high-resolution images of macro-scale regions of the brain. However, the great complexity of neural circuits in the mammalian brain makes manual reconstruction time-consuming and impractical, therefore automation is required to sustain data collection and make significant progress in the field. Nevertheless, automatically extracting a wiring diagram from vast amounts of image data continues to be a challenge for researchers. In this work, we introduce a new computational framework for automated and semi-automated extraction of labeled neurons based on scalar-field topology. We have begun applying this framework to extract single neurons in networks sparsely labeled using an AAV9 carrying the gene for green fluorescent protein in tissue blocks of primate visual cortex cleared using the PACT technique (Yang et al. 2014) and imaged on a 2-photon microscope.
The Morse-Smale complex (MSC) is a multi-scale topological structure that extracts the gradient flow behavior of a scalar-valued function. It contains critical points, such as maxima, saddles, and minima, arcs representing ridge- and valley-like structures, as well as spatial decompositions. Recent advances in the ability to compute the MSC for large data has made

application to neuroscience possible. We compute the MSC and use its critical points and arcs as a scaffolding for subsequent computation of wiring diagrams. The arcs of the MSC initially represent every possible ridge-like structure, recasting the problem of computing wiring diagrams to one of selecting which arcs correspond to axons and dendrites. As the graph structure is computationally light-weight, our system allows a user to adjust filtering thresholds interactively to extract labeled neurons and their processes. We plan to use the MSC to guide manual labeling, with the ultimate goal of full automation through machine learning.




**Disclosures:** **A. Gyulassy:** None. **F. Federer:** None. **A. Venkat:** None. **V. Pascucci:** None. **A. Angelucci:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

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**Program#/Poster#:** 531.06/WW10

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** RO1 EY019743

RO1 EY026812

U01 NS099702

IOS 1355075

EAGER 1649923

U of Utah seed grant 10040877

Research to Prevent Blindness

**Title:** An online system for continuous image acquisition of long-range circuits in cleared primate cortex

**Authors: *A. VENKAT**[1], F. FEDERER[2], C. CHRISTENSEN[1], A. GYULASSY[1], A. ANGELUCCI[2], V. PASCUCCI[1]
[1]Scientific Computing and Imaging Inst., [2]Moran Eye Inst., Univ. of Utah, Salt Lake City, UT

**Abstract:** The primate brain contains billions of interconnected neurons forming complex circuits. The goal of the connectome is to create a wiring diagram of these circuits across the entire brain. Mapping the non-human primate brain at cellular resolution has become feasible due to the emergence of viral-vector-based high-resolution labeling of neurons, optical tissue clearing, and deep tissue imaging. But these advances introduce new challenges for data management and processing. Three such challenges impede the transformation of these datasets into a comprehensive map of neural connectivity: insufficient storage, lack of quality control, and alignment of hundreds of individual volumes. Raw microscopy data can be very large: 1024x1024 resolution images of the entire mouse brain at 20x-magnification are over 31 TB in size, and those of the macaque primary visual cortex (~6,000 $mm^3$), our target, are over 320 TB. Datasets of this size are infeasible to store and process using existing applications on the average PC workstation. More importantly, acquisitions of this size can take weeks or months to complete, yet most software packages don't provide an opportunity to perform any quality checks during acquisition, leading to errors, and thus wasted time and repetition of work. Finally, stitching and alignment of the images into a single volume is required, due to subtle sample movement and microscope stage imprecisions occurring over long acquisition times; but existing software packages for this task have high memory requirements and cannot directly utilize remotely hosted data. In summary, there exists a need for a unified software framework that works in synchronization with the microscope to seamlessly align and store multiple volumes in a format that allows researchers to assess their data quality and begin analysis during the acquisition process.
At SfN 2015, we presented the ViSUS platform addressing the challenges posed by handling large neuronal microscopy data for scalable analysis and visualization (Christensen et al. 2015). We have integrated the ViSUS technology with our two-photon microscope to facilitate online conversion of the image data to a 3d streaming format, allowing uninterrupted acquisition and immediate remote multi-user access to the data. To address the challenge of stitching terabytes of data, we have developed a robust strategy that uses Normalized Cross Correlation to compute 3d pairwise transformations between adjacent tiles during acquisition. This online processing facilitates efficient resource allocation, allowing users to explore and annotate well-aligned 3d volumes while ongoing acquisitions continue without interruption.

**Disclosures:** **A. Venkat:** None. **F. Federer:** None. **C. Christensen:** None. **A. Gyulassy:** None. **A. Angelucci:** None. **V. Pascucci:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.07/WW11

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** NIH Grant MH096093

Harvey Family Endowment

**Title:** Neurocircuitry changes in response to unconditioned fear in mouse models of PTSD

**Authors:** ***A. REVIERE**[1], R. E. JACOBS[2], E. L. BEARER[3,4]
[1]Pathology, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [2]Zilkha Neurogenetic Inst., USC Keck Sch. of Med., Los Angeles, CA; [3]Dept. of Pathology, UNM Sch. of Med., Albuquerque, NM; [4]Biol., Caltech, Pasadena, CA

**Abstract:** Post-traumatic stress disorder (PTSD) is a serious mental illness affecting up to 8% of the general population, including veterans and victims of domestic abuse. Neurological correlates include changes in the amygdala, hypothalamus, hippocampus, and various areas in the prefrontal cortex. We use manganese-enhanced magnetic resonance imaging of mesolimbic circuitry in living mice with SERT, DAT or NET gene knocked out (KO). We showed that the circuitry from the medial forebrain into the limbic system was altered in KO mice compared to WT, although in different ways. We hypothesize that loss of serotonin regulation will prolong neural activity in response to fear. We used exposure to predator odor, (2,3,5-Trimethyl-3-thiazoline) derived from fox anal gland, as a naturalistic validated approach for eliciting fear and leading to PTSD-like symptomology in rodents. WT littermates and SERT KO mice (12 each) were video recorded in a light-dark box, and pre-scanned in an 11.7 T Bruker magnetic resonance scanner to establish baselines. Each mouse was injected with $Mn^{2+}$ IP and scanned 24hr later to detect uptake of $Mn^{2+}$ in active neurons prior to fear provocation. Immediately following mice were exposed first to saline and then to a predator odor. Behavioral effects (freezing, grooming) were monitored. Neural activity was tracked by capturing MR images at 9d, re-injecting with $Mn^{2+}$ IP and re-scanning 24hr later to test for persistence of $Mn^{2+}$ intensity patterns and detect prolonged neural activity levels after fear in KO mice. Behavior in the light-dark box was monitored at each step. Using statistical parametric mapping (SPM) we compared images within-group between timepoints by paired t-tests (p=0.001 uncorr, 0.05 FDR) which detected strong signal in the paraventricular nucleus, hypothalamus and amygdala in SERT KO mice after 10 days compared to their baseline scans which appeared greater than WT. SPM

between group comparisons of $Mn^{2+}$-induced intensity changes demonstrated that location and intensity of neural activation is altered in the SERT KO compared to WT. An ROI analysis was done to determine the extent of difference in voxel intensity between groups at the 10-day timepoint. Activation of these brain regions was confirmed by c-Fos staining in immunohistochemistry of the same mice. The active brain regions elucidated here in the fear-induced SERT KO animals correlate to known behaviors reflecting PTSD-like symptoms such as avoidance and hyperarousal exhibited by these mice in light-dark box behavioral experiments. This is congruous to evidence implicating these areas in PTSD, both in rodents and in humans.

**Disclosures: A. Reviere:** None. **R.E. Jacobs:** None. **E.L. Bearer:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

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**Program#/Poster#:** 531.08/WW12

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** AFOSR Grant FA9550-12-10232

NSF Grant 1544383

Open Science Prize Competition funded by NIH, Wellcome Trust and HHMI

**Title:** NeuroGFX: A graphical functional explorer for fruit fly brain circuits

**Authors: *Y. ZHOU**, C.-H. YEH, N. H. UKANI, A. A. LAZAR
Electrical Engin., Columbia Univ., New York, NY

**Abstract:** Recently, multiple focused efforts have resulted in a substantial increase in the availability of genetic and connectome data for the fruit fly brain. To help infer the function of various *Drosophila* neural circuits from these data, we have developed NeuroGFX, a tool for scalable and collaborative computational modeling, and integrated it into the architecture of the Fruit Fly Brain Observatory (http://fruitflybrain.org) [1].
The computational infrastructure in NeuroGFX is provided by Neurokernel [2], an open source platform for the emulation of the fly brain, and NeuroArch [3], a database for querying and executing fly brain circuits. The integration of the two enables the algorithmic construction and manipulation of executable circuits on multiple levels of abstraction of the fly brain. The power of this computational infrastructure can be leveraged through a graphical user interface that allows visualizing execution results in the context of biological brain structure. This provides an environment where computational researchers can present configurable, executable neural circuits, and experimental scientists can easily explore circuit structure and function ultimately leading to biological validation.

NeuroGFX enables the exploration of the function of neural circuits at the whole brain, neuropil, and local circuit levels of abstraction. We applied NeuroGFX to the implementation of models of the early visual and the early olfactory systems and the central complex of the fly brain. As an example, we show in Fig.1 an executable cartridge circuit in the lamina neuropil of the wild type fly (top) and a reconfigured circuit that models the silencing of certain neurons (bottom). We demonstrate the usage of NeuroGFX for characterizing the I/O of the three systems and their constituent neuropils by executing a variety of underlying circuits.

[1] Ukani NH et al., Neurokernel RFC#7, 2016. DOI: 10.1011/092288.
[2] Givon LE and Lazar AA, *PLoS ONE* 11(1): e0146581, 2016. DOI: 10.1371/journal.pone.0146581.
[3] Givon LE et al., Neurokernel RFC#4, 2015. DOI: 10.5281/zenodo.44225.

**Disclosures:** **Y. Zhou:** None. **C. Yeh:** None. **N.H. Ukani:** None. **A.A. Lazar:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.09/WW13

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** IARPA Contract #D16PC00002

**Title:** Fast learning-free 2D segmentation and 3D reconstruction software for sparse neuronal circuit tracing

**Authors: A. SHAHBAZI**[1], M. JOESCH[2], N. B. KASTHURI[3], *W. SCHEIRER[1]
[1]Computer Sci. and Engin., Univ. of Notre Dame, South Bend, IN; [2]IST Austria, Vienna, Austria; [3]Argonne Natl. Laboratory, Univ. of Chicago, Chicago, IL

**Abstract:** Recent innovations in different types of microscopy have turned imaging into a dominant strategy for data collection in neuroscience. For problems like sparse neuronal circuit tracing, the use of microscopy yields 3D stacks of images that can scale to petabytes of data for a single experiment, depending on the modality. But with this abundance of data has come major challenges in automatic data analysis. Machine learning methods, and especially deep learning-based algorithms, designed to automatically segment and reconstruct structures in the tissue are very slow to train over sets of manually annotated images. Moreover, due to constraints in annotator expertise, time and budget, machine learning models are usually trained on small stacks of manually annotated images instead of sufficiently large training datasets that can better represent the variance in the overall data. This has a negative impact on the resulting accuracy of the software.
Therefore we introduce a new fast learning-free method for automatic sparse 2D segmentation and 3D reconstruction of brain micro-structure. Different from prior supervised methods, our algorithm exploits cell-specific context clues and requires no extensive pre-training. The algorithm combines thresholded filters with graph-based matching to achieve its efficiency. Our approach works on different modalities and sample targets, including serial section electron microscopy of APEX2-positive processes and high-energy synchrotron X-ray microtomography of cortical volumes.
Experiments on newly published and novel mouse data sets demonstrate high precision and recall for the proposed algorithm, as well as reconstructions of sufficient quality for further biological work. Compared to existing supervised and unsupervised methods, it is both significantly faster (up to several order of magnitude) and comparable in segmentation and reconstruction performance.This is true even in cases where staining artifacts, grayscale inconsistency, noise and other artifacts negatively impact the prediction capabilities of machine leaning-based approaches.

Use cases for this new method span a number of different tasks. It can be used to create a first-pass reconstruction of a large area of tissue, or to produce comparison data that can be deployed as a sanity check for machine learning-based methods when ground-truth is not available for evaluation. Further, it is possible to rapidly verify image quality of multi-terabyte image stacks using this approach, and to create imperfect, but very large, training sets for deep learning methods without the need for human intervention.

**Disclosures:** **A. Shahbazi:** None. **M. Joesch:** None. **N.B. Kasthuri:** None. **W. Scheirer:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.10/WW14

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** NIH (DA036400, MH105949, MH105971)

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NSF IIS-1550757

**Title:** Summarization of a brain-wide data set of anterograde tracer injections in mouse using topological skeletonization

**Authors: *S. WANG**[1], X. LI[2], Y. WANG[1], P. P. MITRA[2]
[1]Computer Sci. and Engin., Ohio State Univ., Columbus, OH; [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY

**Abstract:** Following an initial proposal to map brain-wide connectivity at a mesoscopic scale, multiple data sets are now available or are in the process of being acquired in Mouse and Marmoset. The basic data sets contain 3D volumetric whole-brain images of tracer injections placed on a systematic grid spanning the brain. It has been customary to summarize these data sets in the form of regional connectivity matrices. However, such a representation is highly lossy and does not respect the fundamental tree-like morphology of the projection neurons underlying the inter-areal projections. We use computational topology methods, specifically discrete Morse theory, to skeletonize anterograde tracer injections in the form of tree structures rooted at the injection sites. Each such tree represents a consensus of the set of neurons that have somata

located at the injection site. The collection of these tree structures across the brain provide a richer summary of the tracer injection data set than a connectivity matrix.
The skeletonization of a tracer injection includes two main steps: (i) a detection step which serves to de-noise the raw data and retain only automatically detected axonal fragments or arbors, (ii) extraction of so-called 1-stable manifolds via discrete Morse theory. In previous work, we applied step (ii) to raw volumetric data, but encountered computational bottlenecks due to high computational complexity, preventing scaling to whole brains without significant loss of resolution. In the present work we employ a divide and merge approach to reduce the computational cost, and are able to process entire brain volumes without excessive downsampling. We first subdivide input images into smaller 3D tiles and construct the 1-stable manifold within each tile. We then perform a thickening and merging process by leveraging the same discrete Morse framework used to skeletonize data within the individual tiles. We apply this skeletonization procedure to summarize a brain-wide anterograde injection data set from the Mouse Brain Architecture Project containing 930 injections of AAV1/2 spanning the left hemisphere of the Mouse brain. The divide-and-merge works with simplicial complex inputs and may have applications beyond the neuron reconstruction problem.

**Disclosures:** **S. Wang:** None. **X. Li:** None. **Y. Wang:** None. **P.P. Mitra:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.11/DP13/WW15 (Dynamic Poster)

**Topic:** I.06. Computation, Modeling, and Simulation

**Title:** Interactive 3D visualization of terabyte-sized nanoscale brain images at 8K resolution

**Authors: *Y. BANDO**[1,2], K. HIWADA[3], M. KANAYA[4,2], T. ITO[4], S. ASANO[2], M. BOVE, Jr.[2], E. S. BOYDEN[2]
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**Abstract:** Three-dimensional (3D) visualization of microscopy images of the brain facilitates intuitive understanding of neuronal morphology and circuit connectivity. With the advent of readily available super-resolution techniques such as Expansion Microscopy (ExM, Science 347(6221):543-548), nanoscale imaging of large specimens producing terabyte-sized datasets is becoming commonplace. In order to help scientists investigate such large-scale datasets, we implemented a high resolution visualization system with an 8K rendering resolution (7,680 x 4,320 screen pixels), so that millimeter-scale and nanoscale features can be displayed at the same time. The system runs our custom volume renderer on a standard workstation equipped with commodity graphics processing units (GPU) and solid-state drives (SSD), driving an 85” large

format monitor with an optical multi-touch sensor for immersive and direct interaction with visualized datasets. In order to deal with terabyte-sized datasets and the 8K rendering resolution given the currently available off-the-shelf computing hardware, the renderer implements three levels of data caches, the first two of which reside on the GPUs for efficient utilization of the limited GPU memory while the last level is on the CPU main memory as a cache for the SSDs, since datasets we consider are much larger than the main memory. We split datasets into 128 x 128 x 128-voxel cubes along with multi-resolution representation to increase spatial data locality. Asynchronous prefetching of such formatted data combined with the aforementioned caching allows us to keep the data transfer rate to the GPUs, which would otherwise go up to 100 GB/s, well within the effective hardware link speed (PCI Express 3.0, x16 lanes) of around 10 GB/s. To demonstrate the system, we imaged a slice of a mouse hippocampus measuring 1.5 x 0.8 x 0.1 mm using ExM with a Zeiss Lightsheet Z.1 fluorescence microscope, leading to an effective imaging resolution of 60 nm via 4.5x physical specimen expansion. This yielded a 4-color, 5 TB dataset consisting of roughly 25,000 x 14,000 x 2,000 voxels. The rendering speed for this dataset is up to 7 frames per second depending on the viewpoint, allowing the user to interactively rotate and zoom into the dataset. The user can investigate the brain sample at a 60 nm resolution while maintaining a large portion of the sample (0.5 mm horizontal) on display, thereby keeping a good sense of cellular context and spatial orientation. Even when zoomed out and the entire dataset fits within the screen, the individual screen pixels still correspond to 180 nm at the specimen level, providing macroscopic and microscopic views simultaneously.

**Disclosures: Y. Bando:** None. **K. Hiwada:** None. **M. Kanaya:** None. **T. Ito:** None. **S. Asano:** None. **M. Bove:** None. **E.S. Boyden:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on patents (assigned to MIT) on ExM and related technologies, Co-founder of a company, Expansion Technologies, aimed at helping disseminate ExM to the scientific community.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 531.12/WW16

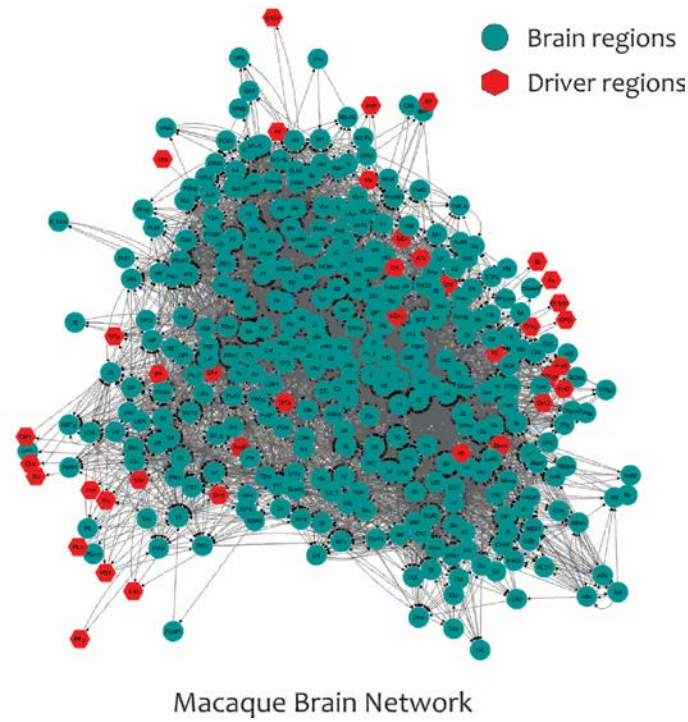
**Topic:** I.06. Computation, Modeling, and Simulation

**Title:** Identification of driver regions in macaque brain network using controllability analysis

**Authors: *V. TRIPATHI**[1], R. BADHWAR[2], G. BAGLER[1]
[1]Ctr. for Computat. Biol., Indraprastha Inst. of Information Technol., Delhi, India; [2]Dept. of Biosci. and Bioengineering, Indian Inst. of Technol. Jodhpur, Jodhpur, India

**Abstract:** Cognitive state of brain is an emergent property arising out of interactions among brain regions. Neuronal connections serve as conduits of communication forming the underlying architecture giving rise to brain functions. Structural controllability analysis is a promising method for investigating control mechanisms of brain network and for finding 'driver regions' that are central to its control. Neuronal connectivity has been investigated for various animal systems including *C. elegans*, drosophila, zebra fish, cat and macaque. Within the limited data available, these studies have probed the structural organization and circuits in an attempt to infer their functional relevance. By investigating controllability of *C. elegans* neuronal network, the only complete connectome available till date, earlier studies have identified and characterized its driver neurons. *Macaca mulatta* is an extensively studied model organism having neuroanatomy very close to that of human. Tract tracing studies of macaque brain have been compiled in an accessible database called CoCoMac.

We constructed the Macaque Brain Network (MBN) using data from CoCoMac that encodes directional connectivity of brain regions. MBN comprises of 6602 directed connections among 360 brain regions spanning the brain. This network was observed to have small world nature with an exponential connectivity distribution. Using controllability analysis, we identified a total of 39 (24 distinct) 'driver regions' that are critical for achieving full control over the state of the network. Among them the major brain regions are: Thalamus, Prefrontal Cortex, Motor cortex, Caudal SMA, Broca's area, Granular retrolimbic area, Dorsolateral visual cortex, Orbitofrontal cortex, Visual area 3A, Amygdala, Posterior parietal area, Prestriate cortex, and Ventral occipito temporal area. These regions, associated with vision, attention, memory, motor, speech, information relay and sensory integration, emerged as critical for driving the brain network in any desired cognitive state.




Macaque Brain Network

**Disclosures:** **V. Tripathi:** None. **R. Badhwar:** None. **G. Bagler:** None.

**Poster**

**531. Computational Tools for Circuit Mapping**

**Location:** Halls A-C

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**Program#/Poster#:** 531.13/WW17

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** NIH Grant R01 MH110932R01

**Title:** Multiscale general purpose segmentation pipeline for connectomics

**Authors: *H. LI**[1], R. VESCOVI[2], M. DU[3], V. DE ANDRADE[4], D. GURSOY[4], S. MIKULA[5], W. SCULLIN[4], V. VISHWANATH[4], C. JACOBSEN[3], N. B. KASTHURI[1]
[1]Neurobio., [2]Biol. Sci. Dept., Univ. of Chicago, Chicago, IL; [3]Northwestern Univ., Evanston, IL; [4]Argonne Natl. Lab., Lemont, IL; [5]Electrons - Photons - Neurons, Max-Planck Inst. For Neurobio., Martinsried, Germany

**Abstract:** In the field of connectomics, a central goal is to reconstruct neural anatomical structure and synaptic connectivity from 3D volumetric data collected by applying various imaging techniques. With recent advancements in automated serial electron microscopy(EM) and micron-resolution Xray tomography(uCT), our ability to acquire images has increased tremendously in both resolution(10nm for EM, 1um for uCT) and volume(1mm2 for EM, 1cm2 for uCT). However, the amount and variety of data pose great computational challenges to our ability to process, analyze and approach biological questions.
A major part of the pipeline is to segment various features of interest from data of various modalities. Recent works often approach segmentation problem with a supervised deep neural network. We propose an end-to-end multi-purpose segmentation pipeline for neural data analysis based on fully convolutional neural networks. For uCT data, we are interested in segmenting cell bodies, blood vessels, and myelinated axons with the goal of reconstructing a coarse neural anatomical map, while for EM data, with much higher resolution, we focus on cell membranes and mitochondria which lead to full segmentation of neurites. We are also exploring solutions to several major challenges in connectomics: 1. Reliance on laborious manual labelling. We have developed a semi-automated training label preparation scheme that allows fast label proposal generation and minimal human correction. 2. Low transferability between different learning sessions. We observed that networks trained for EM and uCT share some resemblance in early layers. Also our fully convolutional design allows arbitrary input data size and retraining with data from different sources, which reuses trained weights and saves training time. 3. Swiftness in designing new neural network architecture. We used a highly modular design in generating neural networks, which allows easy generation of specialized neural networks for different scenarios and rapid testing. Apart from algorithm design, another push is to deploy and optimize the pipeline on high performance computing facilities.

**Disclosures:** **H. Li:** None. **R. Vescovi:** None. **M. Du:** None. **V. de Andrade:** None. **D. Gursoy:** None. **S. Mikula:** None. **W. Scullin:** None. **V. Vishwanath:** None. **C. Jacobsen:** None. **N.B. Kasthuri:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.01/WW18

**Topic:** I.07. Data Analysis and Statistics

**Support:** DARPA SUBNETS Grant W911NF-14-2-0045

**Title:** An open-source, general-purpose software toolkit for analysis of dynamical behavioral signals

**Authors: *A. YOUSEFI**[1], Y. LEI[2], D. D. DOUGHERTY[3], E. N. ESKANDAR[4], A. S. WIDGE[5], U. EDEN[6]
[1]Dept. of Neurosurg., MGH, Boston, MA; [2]Neurosurg., [3]Psychiatry, Harvard Med. Sch., Boston, MA; [4]Neurosurg., Massachusetts Gen. Hosp., Boston, MA; [5]Psychiatry, Massachusetts Gen. Hosp., Charlestown, MA; [6]Mathematics and Statistics, Boston Univ., Boston, MA

**Abstract:** Computational models have been an integral part of the analysis of dynamical behavioral signals. These models are widely used in clinical and basic neuroscience research to infer underlying mental or cognitive states that shape behavior and study their correlates brain dynamics. Despite the importance of these models, a significant challenge is their development. Development of these models generally gets complicated and requires an extensive time for debugging and verification. A general modeling software toolbox would help researchers to perform their analysis without extensive code development, and would also provide a medium to assess parallel research outcomes. In this research, we introduce a computational modeling toolbox suitable for analysis of dynamical behavior signals. The toolbox utilizes a state-space modeling framework, which can model and process dynamical behavioral and physiologic signals from many modalities. The modeling output using the toolbox not only includes an estimate of the latent variables of interest, but also provides a set of goodness-of-fit analysis, which might be used in assessment and refinement of the models. Under the state-space modeling assumption, the mental or cognitive state dynamics over time is represented by the state-equation, and the behavioral signals are the observation process. The toolbox estimates both model free parameters and underlying mental or cognitive state. Behavioral signals might be a continuous signal such as reaction time, a discrete signal like decision choice, or a combination of continuous and discrete signals. Models can be fit to behavioral signals with Normal, Gamma, or Bernoulli (binomial) distributions, as well as mixtures of continuous and discrete distributions. The toolbox has utilities to deal with missing or censored data points. We demonstrate the

toolbox application in analysis of two different behavioral tasks. The first task is an associative learning task, where a subject learns multiple associations simultaneously. The objective is to infer a single "learning state" that estimates how well the overall set of associations has been learned, optimally integrating performance over all available stimuli. The second task is an approach-avoidance task designed to analyze schizophrenia patients' sensitivity to loss and reward. The objective is to combine common reinforcement learning models, "actor-critic" and "Q-learning", with the key parameter controlling how much each model drove behavior. We show the step-by-step implementation of these models using the toolbox, and we further discuss goodness-of-fit analysis and modeling result interpretation.

**Disclosures:** **A. Yousefi:** None. **Y. Lei:** None. **D.D. Dougherty:** None. **E.N. Eskandar:** None. **A.S. Widge:** None. **U. Eden:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.02/WW19

**Topic:** I.07. Data Analysis and Statistics

**Support:** HHMI

DARPA

NIH

Helen Hay Whitney Foundation

**Title:** Maximum likelihood based cell sorting of large-scale neural calcium imaging data

**Authors: *B. AHANONU**[1,2,3], L. J. KITCH[3], T. H. KIM[3], M. C. LARKIN[3], E. O. HAMEL[3], J. LECOQ[4], M. J. SCHNITZER[1,2,3]
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**Abstract:** Recent advances in large-scale neural calcium imaging allow neuroscientists to visualize the concurrent dynamics of hundreds to thousands of individual neurons in live animals, but analysis of these datasets remains a bottleneck. Existing methods for extracting individual cells and their activity traces from calcium imaging datasets have several limitations, including inherent tradeoffs between signal detection fidelity and crosstalk between nearby cells. To date, no algorithm has demonstrated the requisite speed, scalability, accuracy, and versatility to provide a general solution. Here we present CELLMax (Cell Extraction by Log Likelihood Maximization), a high-fidelity cell extraction method that makes no assumptions about the

temporal structure of cells' activity traces. The algorithm is highly parallelizable, and under suitable conditions its runtime scales sub-linearly with dataset size. To demonstrate the statistical optimality of CELLMax, we show that its estimator variance approaches the mathematical lower bound and that the algorithm achieves a maximum likelihood solution. In validation studies with simulated datasets, we found that CELLMax generally yielded superior estimates of cells' fluorescence activity traces as compared to the most commonly used cell sorting algorithms. In studies with real data acquired in the hippocampus of freely behaving mice, neural activity traces extracted by CELLMax allowed superior positional estimates of the mouse's running trajectory. Overall, our results show that CELLMax is a versatile, reliable, and scalable approach for extracting cellular signals from a wide variety of calcium imaging datasets; thus, we expect its usage should help improve the pace and accuracy of experiments relying on large-scale neural calcium imaging.

**Disclosures: B. Ahanonu:** None. **L.J. Kitch:** None. **T.H. Kim:** None. **M.C. Larkin:** None. **E.O. Hamel:** None. **J. Lecoq:** None. **M.J. Schnitzer:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.03/WW20

**Topic:** I.07. Data Analysis and Statistics

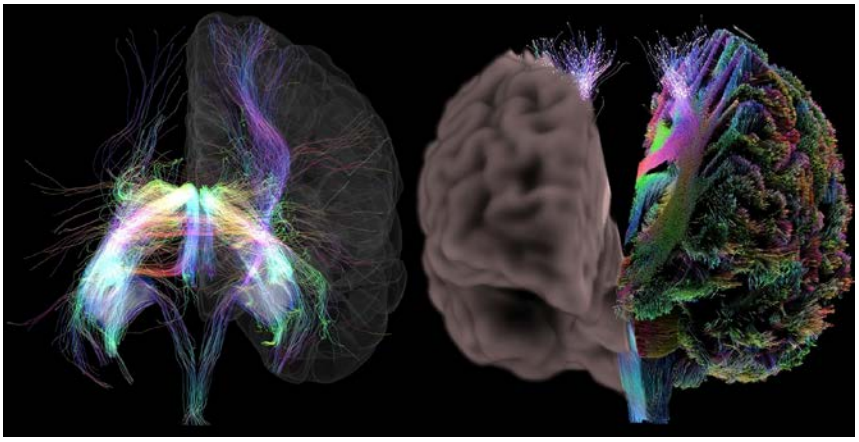
**Support:** P41-EB015922

**Title:** Utilizing state of the art rendering techniques and virtual reality to better visualize neuroscientific data

**Authors: *T. D. ARD**, J. STANIS, D. DUNCAN, A. W. TOGA
USC Stevens Neuroimaging and Informatics Inst., Los Angeles, CA

**Abstract:** Visualization is a critical component in neuroscientific investigation, enabling researchers to intuitively understand and meaningfully navigate complex data. This is becoming even more crucial as methodologies such as magnetic resonance imaging (MRI) and microscopy advance in spatial and temporal scales, resulting in truly massive and unwieldy datasets. While these large datasets hold the key in unlocking the next generation of breakthroughs, they pose unique challenges for comprehension and visualization. We have developed software that bridges state of the art graphical, cinematic, and gaming industry technology with very large neuroimaging datasets, creating several novel tools to better visualize and explore cellular and neuroimaging data, both in and outside of virtual reality (VR). Outside of virtual reality, our novel MRI visualizations include a new approach to visualizing diffusion imaging through particle motion, functional MRI rendering through sparse particle clouds, and advances in

tractography and structural rendering demonstrating all of the fine detail available in high-field MRI. Additionally our novel cellular visualization techniques are able to reconstruct, enhance, and portray large-scale datasets in a navigable manner while maintaining the ability to portray perceivable fine cellular structures. Inside virtual reality, we've leveraged VR's intuitive spatial exploration and 3D display capabilities to offer optimal navigation of neuroscientific data. By employing various real-time rendering techniques we can navigate volumetric MRI data and extracted surfaces from individual subjects as a 'virtual dissection.' Furthermore we can view tractography data, as well as cellular structure and datasets in their natural 3D setting to more accurately and naturally comprehend their 3D structure. Overall, our visualization software begins to modernize neuroscientific data visualization, offering more comprehensive, navigable and detailed exploration of large and complex datasets.



**Disclosures:** **T.D. Ard:** None. **J. Stanis:** None. **D. Duncan:** None. **A.W. Toga:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.04/WW21

**Topic:** I.07. Data Analysis and Statistics

**Support:** EU H2020 grant agreement No. 720270 (Human Brain Project)

EU H2020 grant agreement No. 654148 (Laserlab-Europe)

EU H2020 ERC grant agreement n. 692943 BrainBIT

Italian Ministry for Education, University, and Research, Flagship Project NanoMAX

Ente Cassa di Risparmio di Firenze

**Title:** Software tools for high-throughput stitching and processing of micron-resolution 3D images of brain samples

**Authors: *G. MAZZAMUTO**[1], L. SILVESTRI[1,2], P. FRASCONI[3], L. SACCONI[1,2], F. S. PAVONE[1,2]
[1]European Lab. For Non-Linear Spectroscopy, Sesto Fiorentino, Italy; [2]Natl. Inst. of Optics (INO-CNR), Sesto Fiorentino, Italy; [3]Dept. of Information Engin. (DINFO), Univ. of Florence, Florence, Italy

**Abstract:** Whole-brain imaging using advanced high-resolution microscopy techniques such as Light-Sheet Fluorescence Microscopy and Two-Photon Fluorescence Microscopy produces big amounts of volumetric data. Microscopic imagery of brain tissues acquired with such techniques include a wealth of valuable information that needs to be processed in an automatic fashion to produce reliable quantitative results. We developed a software pipeline that allows us to perform different levels of processing including: stitching of overlapping 3D tiles, cell counting, cell segmentation, vascular segmentation.
The first and most delicate step in the pipeline is tile stitching. Given the extent of our datasets (several TB of data) and the need for high-throughput processing, we found that existing open source software solutions do not perform and scale well. On the other hand, commercial software products for image stitching already exist, but these are costly and closed source. Our dedicated stitching tool computes optimal alignment of adjacent tiles by evaluating the cross-correlation of overlapping areas at selected stack depths. This ensures a high throughput, since a large dataset need not be processed in its entirety. Furthermore, cross-correlation is computed efficiently by means of FFT. The software is fully written in Python and makes use of state of the art computing libraries. The tool exposes a public Application Programming Interface (API) that can be used to perform queries on the stitched dataset for further processing.
In the second stage of processing, stitched images produced with the software tool described above are fed to cell segmentation, identification and counting algorithms based on machine learning. Here, high throughput is obtained by exploiting the parallel computing capabilities of modern GPUs.

**Disclosures: G. Mazzamuto:** None. **L. Silvestri:** None. **P. Frasconi:** None. **L. Sacconi:** None. **F.S. Pavone:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.05/WW22

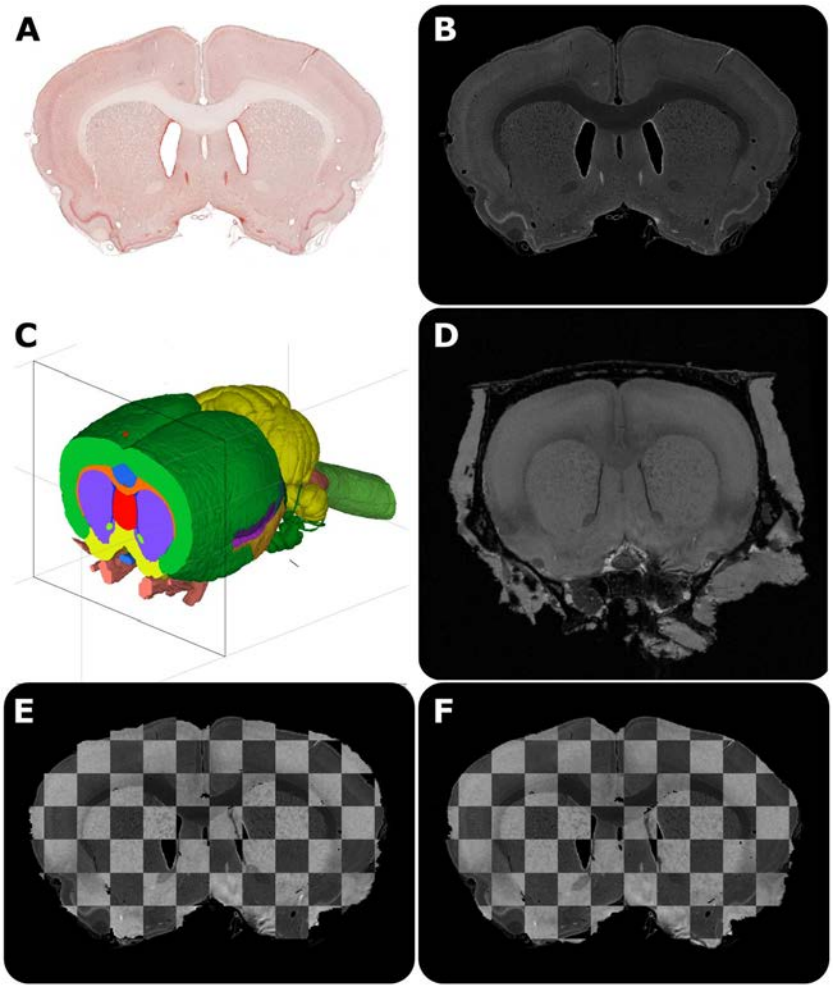
**Topic:** I.07. Data Analysis and Statistics

**Support:** EU Horizon 2020, Human Brain Project, Grant 720270

**Title:** Tackling the normalization of 2-D rodent histology sections in a 3-D coordinate space

**Authors: C. COELLO**, T. B. LEERGAARD, *J. G. BJAALIE
Inst. of Basic Med. Sci., Univ. of Oslo, Oslo, Norway

**Abstract:** The increasing deluge of reported experimental neuroscience data calls for efficient approaches to integrating and comparing data. The new generation of 3-D rodent brain reference atlases and accompanying tools provide new opportunities for spatial co-registration (integration) and comparison of different types of brain images, including microscopic images of serial sections through the brain. Spatial registration of serial 2-D section images to a 3-D reference space using affine transformations is useful and relatively practical to implement, whereas non-linear and thus potentially more accurate methods are complex and in most cases require spatially coherent input data. 3-D reconstruction of serial 2-D images is manageable if block face imaging is used, but otherwise quite tedious. We here present a methodological framework to non-linear registration of purely 2-D (not spatially coherent) images to 3-D space. The framework is built to address variability in acquisition parameters (cutting plane, single section or stack, number of slices in a stack, distance between successive slices, etc⋯) between experiments. We initially employ a global manual anchoring of the section material (Figure 1A) within the reference coordinate space (step 0) followed by estimation of a multi-level transformation using intensity- and/or landmark- similarity metrics (step 1). The transformation model was selected as diffeomorphic and calculated between the transformed source (Figure 1B) and the resliced target (Figure 1C and 1D) at the level given by the initial anchoring step (2-D to 2-D). The combination of global anchoring followed by multi-level transformation (Figure 1F) perform similarly or better than anchoring only (Figure 1E) at normalizing individual 2-D slices to a 3-D space at the cost of additional pre-processing steps that we aim to automatize to facilitate the use of this spatial integration framework.




**Disclosures:** **C. Coello:** None. **T.B. Leergaard:** None. **J.G. Bjaalie:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.06/WW23

**Topic:** I.07. Data Analysis and Statistics

**Title:** A semi-automated lesion mapping approach for rhesus macaques

**Authors: *M. PUJARA**[1,2], E. A. MURRAY[2]
[1]NIH, Bethesda, MD; [2]Natl. Inst. of Mental Health, NIH, Section on the Neurobio. of Learning and Memory, Lab. of Neuropsychology, Bethesda, MD

**Abstract:** Studies of rhesus macaques (*Macaca mulatta*) with intended focal brain lesions provide critical insights on the relationships between brain structure and behavior. Current techniques allow researchers to damage cell bodies selectively, while sparing fibers of passage. A major challenge of the lesion method in rhesus macaques is documenting the degree to which the lesion is both complete and selective for the region of interest. Currently, lesion extent is manually drawn on a series of sections of a reference brain from visual inspection of a postoperative T1 MRI scan (in which damage appears as relative hyposignal), T2 MRI scan (in which damage appears as relative hypersignal), or histology slides. However, this approach is time-consuming and difficult to standardize. Recent advances in automated nonlinear registration algorithms and the advent of a standard template for rhesus macaques (Seidlitz, Sponheim, et al 2017) may improve the speed and standardization of lesion mapping via automated registration of a monkey's lesion to a common anatomical reference space. Here, we employ a semi-automated method to map cortical lesion boundaries (e.g., orbitofrontal cortex, prelimbic cortex, premotor cortex) from multiple subjects to a single standard template. This two-step process involves: 1) manually tracing the lesions in native space on the subject's postoperative MRI scan, and 2) warping the traced lesion mask and postoperative scan to template space using a nonlinear algorithm provided by a validated neuroimaging software package, ANTs (Avants et al, 2010). We further evaluate the extent to which the damage registered in the *in vivo* scans are representative of the actual surgical damage by comparing these digitized masks to traditional Nissl-stained histological material. This approach provides an improved method for lesion mapping that saves time, standardizes results, and provides multiple options for quantifying lesion extent and generating informative 2D and 3D visualizations.

**Disclosures: M. Pujara:** None. **E.A. Murray:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.07/WW24

**Topic:** I.07. Data Analysis and Statistics

**Support:** NIMH Intramural Research Program

**Title:** NIMH MonkeyLogic 2: Open source experimental control and data acquisition

**Authors: *J. HWANG**[1], A. R. MITZ[2], E. A. MURRAY[1,2]
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**Abstract:** MonkeyLogic (ML1) is an open source MATLAB (Mathworks) toolbox for complex behavioral control and data acquisition with sub-millisecond temporal precision (Asaad &

Eskandar, 2008). To date, ML1 has been cited in >50 peer-reviewed publications and is used by >30 research groups worldwide. However, ML1 does not support the 64-bit computing environment and has incompatibility issues with MATLAB's new HG2 graphics engine. In addition, ML1 requires the MATLAB Data Acquisition Toolbox and two identical interface boards to operate at full speed. We now report the development of NIMH MonkeyLogic 2 (ML2), which resolves these key issues and adds new features to broaden the user base.
ML2 fully supports the 64-bit MATLAB environment and the latest versions MATLAB, while keeping nearly full compatibility with ML1 behavioral task files. The cost for implementing ML2 is significantly less than ML1 for two reasons. First, because ML2 requires only one interface board to achieve sub-millisecond timing precision, whereas ML1 required two, moving from ML1 to ML2 will free-up an interface card and thereby reduce the cost of running a new ML2 installation for existing users. Second, the MATLAB Data Acquisition Toolbox is no longer needed. It has been replaced by a new, open-source NIMH Data Acquisition Toolbox (NIMH DAQ), which both reduces the cost and greatly enhances performance. ML2 also uses a new NIMH MonkeyLogic Graphics Library (MGL) that draws both subject and control screens with hardware accelerated application programming interfaces. As a result, ML2 has rapid control screen updates so that the experimenter's control screen can reproduce the graphics seen on the subject's screen.
In sum, ML2 has improved timing precision, supports transparent images, has a greater analog channel count and supports multiple new input devices (e.g., touchscreens, USB joysticks). ML2 also employs a more efficient and flexible data file structure without sacrificing backward compatibility at the MATLAB programming level. Examples and benchmark results will be presented along with a more complete description of the changes.

**Disclosures: J. Hwang:** None. **A.R. Mitz:** None. **E.A. Murray:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.08/WW25

**Topic:** I.07. Data Analysis and Statistics

**Support:** Research supported by the European Commission through the Marie Curie European Joint Doctorate 'Complex oscillatory systems: Modeling and Analysis (COSMOS)', project 642563.

**Title:** Using spike train distances to evaluate neuronal population coding, Part II

**Authors: *E. A. SATUVUORI**[1,2,3], M. MULANSKY[2], T. KREUZ[2]
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Italy; [3]MOVE Res. Institute, Dept. of Human Movement Sciences,, Vrije Univ. Amsterdam, Amsterdam, Netherlands

**Abstract:** This part II continues from the greedy algorithm introduced in part I [1]. The Victor-Purpura distance and the van Rossum distance extensions for population coding [2, 3] use a parameter to scale between labelled line coding (LLC), where each neuron is treated separately, and summed population coding (SPC), where all spikes are pooled and the identity of the neuron that emitted the spike is not important.
Instead of simply taking a set of spike trains and assuming that the all the recorded neurons are coding neurons, we here identify the best performing subpopulation using the SPIKE-distance. We test two versions of greedy algorithms presented in Part 1 together with a new heuristic simulated annealing algorithm, that provides significantly faster analysis times when compared to brute force solutions but evaluates many more subpopulations and is thus considerably slower than the greedy algorithm.
In order to assess the performances of our algorithms we use small enough test sets so that brute force is feasible and the correct solutions can be used as reference point to search for situations in which each algorithm is not able to reach the globally optimal solution. To test the algorithms, we use Poisson neurons with different levels of noise. For the LLC population, we limit our study to discrimination between different stimuli with minimum number of neurons and identify the SPC population by using our new algorithms.
The measures of spike train synchrony ISI-distance [4], SPIKE-distance [5] and SPIKE Synchronization [6] as well as the new directional measure SPIKE-Order [7] are freely available in the Matlab-based graphical user interface SPIKY [6], the Matlab command line package cSPIKE, and the Python library PySpike [8]. Source codes of SPIKY, cSPIKE, and PySpike are available at [9,10,11].
[1]Kreuz T, Satuvuori E,and Mulansky M SfN abstract (2017)
[2]Aronov D, Reich DS, Mechler F, Victor JD. J Neurophysiol 89, 3304 (2003)
[3]Houghton C, Sen K. Neural Computation 20, 1495 (2008)
[4]Kreuz T, Haas JS, Morelli A, Abarbanel HDI, Politi A. J Neurosci Methods 165, 151 (2007)
[5]Kreuz T, Chicharro D, Houghton C, Andrzejak RG, Mormann F. J Neurophysiol 109, 1457 (2013)
[6]Kreuz T, Mulansky M, Bozanic N, JNeurophysiol 113, 3432 (2015)
[7]Kreuz T, Satuvuori E, Pofahl M, Mulansky M. New J Phys 19, 043028 (2017).
[8]Mulansky M, Kreuz T. Software X 5, 183 (2016)
[9]http://www.fi.isc.cnr.it/users/thomas.kreuz/Source-Code/SPIKY.html
[10]http://www.fi.isc.cnr.it/users/thomas.kreuz/Source-Code/cSPIKE.html
[11]https://github.com/mariomulansky/PySpike

**Disclosures: E.A. Satuvuori:** None. **M. Mulansky:** None. **T. Kreuz:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.09/WW26

**Topic:** I.07. Data Analysis and Statistics

**Support:** European Commission: Marie Curie European Joint Doctorate 'Complex oscillatory systems: Modeling and Analysis (COSMOS)', project 642563

**Title:** Using spike train distances to evaluate neuronal population coding, part I

**Authors: *T. KREUZ**[1], E. A. SATUVUORI[2], M. MULANSKY[1]
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**Abstract:** During the last decade spike train distances **[1-4]** have become an essential means to characterize neural coding in a wide range of neurophysiological contexts. In a typical setup different stimuli are presented repeatedly and a pairwise similarity analysis is carried out to evaluate whether responses to the same stimulus exhibit smaller distances than responses to different stimuli. With the increasing availability of multi-neuron recordings these kinds of analyses can now be performed not just for individual neurons but rather for simultaneously recorded neuronal populations.
The bivariate Victor-Purpura and the van Rossum distance **[1, 2]** have been extended to quantify dissimilarities between multi-unit responses. These population measures **[5, 6]** estimate the discrimination performance of either the population as a whole (summed population) or of individual neurons (labelled line). However, if the two extremes fail, these approaches do not answer the question which subpopulation within the larger population discriminates the presented stimuli best.
The brute-force approach of evaluating every possible neuronal subpopulation is not feasible. Thus, in the first part of this study we follow a complimentary approach and present an iterative algorithm which considerably restricts the number of subpopulations for which the pairwise distance matrices and the stimulus discrimination performance have to be calculated. The second part of this study proposes a simulated annealing approach **[7]**.
The three measures ISI-distance **[3]**, SPIKE-distance **[4]** and SPIKE-Synchronization **[7]** as well as the new directional measure SPIKE-Order **[9]** are implemented in the Matlab-based graphical user interface SPIKY **[8]**, the Matlab command line library cSPIKE, and the Python library PySpike **[10] [11]**.
[1] Victor J, Purpura K. *J Neurophysiol* **76**, 1310 (1996)
[2] van Rossum MCW. *Neural Computation* **13**, 751 (2001)
[3] Kreuz T, Haas JS, Morelli A, Abarbanel HDI, Politi A. *J Neurosci Methods* **165**, 151 (2007)
[4] Kreuz T, Chicharro D, Houghton C, Andrzejak RG, Mormann F. *J Neurophysiol* **109**, 1457

(2013)
[5] Aronov D, Reich DS, Mechler F, Victor JD. *J Neurophysiol* **89**, 3304 (2003)
[6] Houghton C, Sen K. *Neural Computation* **20**, 1495 (2008)
[7] Satuvuori E, Mulansky M, Kreuz T, *SFN abstract* (2017)
[8] Kreuz T, Mulansky M, Bozanic N, *J Neurophysiol* **113**, 3432 (2015)
[9] Kreuz T, Satuvuori E, Pofahl M, Mulansky M. *New J Phys* **19**, 043028 (2017).
[10] Mulansky M, Kreuz T. Software X **5**, 183 (2016)
[11] http://www.fi.isc.cnr.it/users/thomas.kreuz/Source-Code/SPIKY.html, http://www.fi.isc.cnr.it/users/thomas.kreuz/Source-Code/cSPIKE.html and https://github.com/mariomulansky/PySpike

**Disclosures: T. Kreuz:** None. **E.A. Satuvuori:** None. **M. Mulansky:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.10/WW27

**Topic:** I.07. Data Analysis and Statistics

**Title:** A novel approach to biomarker discovery through conceptual integration of multimodal datasets

**Authors: H. UNG**, M. C. HOLLENBECK, A. CHRISTINI, *J. B. WAGENAAR
Blackfynn Inc., Philadelphia, PA

**Abstract:** Biomarker discovery in large-scale multimodal datasets requires a thorough understanding of the underlying data, its structure, and their relationships. Data preparation to explore these relationships for analysis is a significant barrier to testing hypotheses and validating existing findings. Recent advancements in multimodal analyses have shown promising results, yet mapping between data modalities is often a difficult task. The ability to easily explore multimodal relationships significantly improves a researcher's ability to generate hypothesis and construct models for discovering novel biomarkers.
Here, we describe a use case for the integration and analysis of a large-scale public multimodal dataset. The Parkinson's Progression Markers Initiative (PPMI) dataset consists of over 600 subjects with imaging, genomics, and behavioral data. Concepts were abstracted from these data using a graph representation, which links individual subjects to modality-specific features. The conceptual mapping and integration of these data were conducted using the Blackfynn scientific data management platform, which enables intelligent data exploration with integrated variable ranking and efficient machine learning analysis. Using the platform, we performed supervised machine learning analysis on the multimodal dataset to classify early Parkinson's versus healthy controls with greater than chance accuracy. From the constructed models, we identified key

features that drove our predictions, which included previously published CSF biomarkers in addition to novel biomarkers that may warrant further investigation.
This use case provides an example of how conceptual multimodal data integration significantly improves the ability of the researcher to discover biomarkers from multi-modal datasets, and how novel platform technologies can facilitating data exploration and scientific analysis.

**Disclosures:** **H. Ung:** A. Employment/Salary (full or part-time):; Blackfynn Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackfynn Inc. **M.C. Hollenbeck:** A. Employment/Salary (full or part-time):; Blackfynn Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackfynn Inc. **A. Christini:** A. Employment/Salary (full or part-time):; Blackfynn Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackfynn Inc. **J.B. Wagenaar:** A. Employment/Salary (full or part-time):; Blackfynn Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackfynn Inc..

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.11/DP15/WW28 (Dynamic Poster)

**Topic:** I.07. Data Analysis and Statistics

**Support:** the Intramural Research Program of the NIH, NINDS

**Title:** A digital 3D atlas set of the marmoset brain based on multimodal MRI

**Authors: *C. LIU**[1], F. Q. YE[2], C. C.-C. YEN[3], J. D. NEWMAN[4], A. C. SILVA[5]
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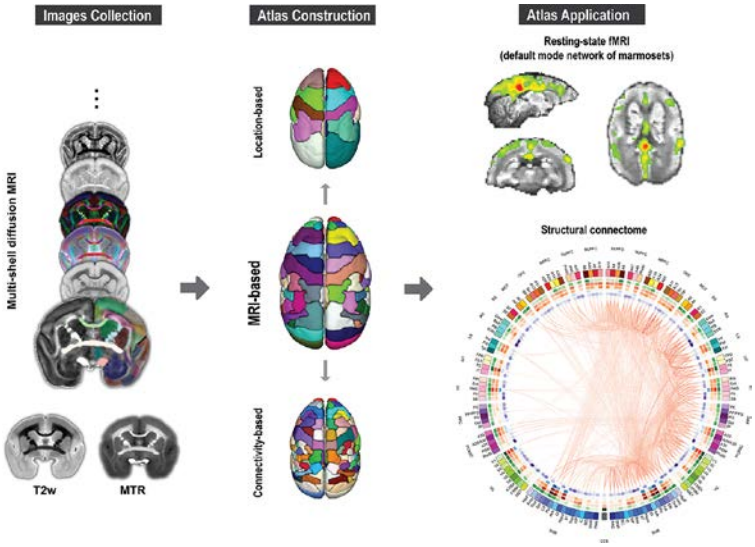
**Abstract:** The common marmoset has become a valuable primate model in neuroscience research. Neuroimaging techniques, especially magnetic resonance imaging (MRI), are essential tools to unveil the anatomical and functional organization of the brain. To facilitate identification of regions of interest (ROI) in the MRI images, it is desirable to register the MRI images to an atlas of the brain. However, all of the currently available atlases of the marmoset brain are based on two-dimensional histological data, which are difficult to be applied to 3D MRI and connectome studies. Here, we constructed a 3D digital atlas set of the marmoset brain that is based on high-resolution ex-vivo MRI images. The atlas was constructed from MRI acquired with different contrasts, including magnetization transfer ratio (MTR, a T1-like contrast), T2-

weighted images, and multi-shell diffusion MRI. Based on the manifold contrasts provided by multimodal images, we manually delineated 54 cortical areas and 16 subcortical regions per brain hemisphere (version 1; MRI-based). The 54 cortical areas were merged into 13 larger cortical regions according to their spatial locations and hierarchical organizations (version 2; location-based). Meanwhile, we also mapped the detailed connectivity profiles of each cortical area based on MR diffusion tractography, and refined the original 54 cortical areas into 106 subregions (version 3; connectivity-based), using a connectivity-based parcellation method that was optimized for the marmoset brain. These three atlas versions are designed for neuroimaging studies of different purposes. Finally, we evaluated the reliability of the atlas across different individuals and demonstrated its application in current studies using diffusion tractography, resting state functional connectivity and connectome analyses. Featured by multimodal contrasts and multilevel parcellations, the atlas set provides a readily usable template space with anatomical labels that can facilitate various current and future neuroimaging studies of marmosets.




**Disclosures:** **C. Liu:** None. **F.Q. Ye:** None. **C.C. Yen:** None. **J.D. Newman:** None. **A.C. Silva:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.12/WW29

**Topic:** I.07. Data Analysis and Statistics

**Support:** European Union’s Horizon 2020 Research and Innovation Programme under Grant Agreement No. 720270 (HBP SGA1)

Norwegian Node of the International Neuroinformatics Coordinating facility

**Title:** QuickNII: Neuroinformatics tool and workflow for anchoring of serial histological images in rodent brain 3D space

**Authors: *M. PUCHADES**, G. CSUCS, M. CHECINSKA, M. ØVSTHUS, I. E. BJERKE, K. ANDERSSON, T. B. LEERGAARD, J. G. BJAALIE
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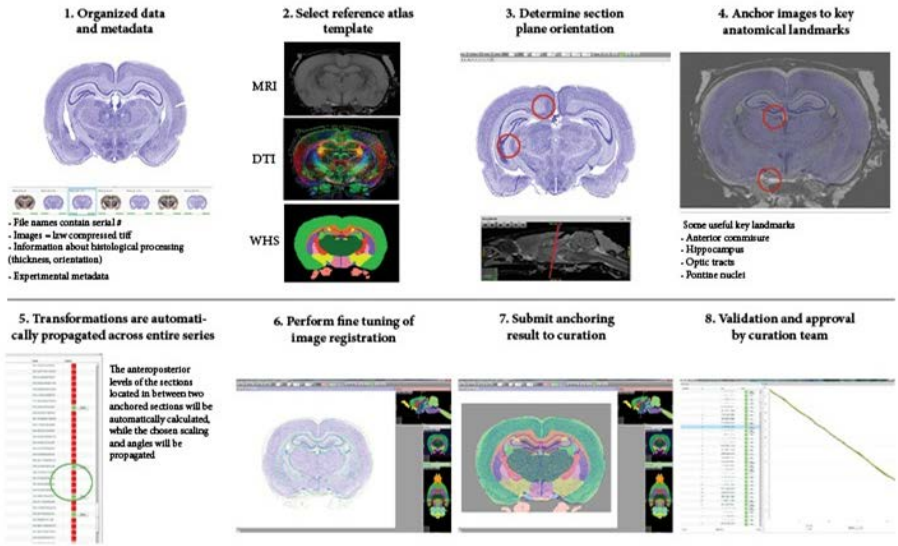
**Abstract:** Reference atlases of the brain are important tools for assigning location to data captured in neuroscience experiments. Spatial alignment of histological section images to reference atlases is challenging to perform for several reasons. Manual approaches are time consuming when applied to large series (e.g., brain-wide) of images and, moreover, histological sections are often cut at angles deviating from the principal anatomical planes presented in conventional reference atlases. Novel 3D reference atlases and accompanying tools provide new opportunities for rapid and accurate spatial registration and integration of data in common reference atlas space. We here present QuickNII, a new tools for use with the Waxholm Space atlas for the rat brain and the Allen brain atlas for the mouse brain, and a workflow allowing users to 1) interactively generate customized atlas images (slices of the 3D reference atlas) corresponding to the plane of sectioning of any experimental image series, 2) superimpose atlas images onto experimental images using affine transformations to match key anatomical landmarks, 3) propagate the transformations across a series of images, 4) assign spatial reference atlas coordinates to the experimental images, and 5) allow viewing and analysis of the experimental data integrated in the reference atlas. We exemplify the workflow and use of our methods with a range of experimental data from neuroanatomical and neurophysiological investigations. The method has been extensively tested on a large number of different image series in several laboratories, and has been shown to be practical and efficient in use. The tool is available from the Neuroimaging Informatics Tools and Resources Clearinghouse (www.nitrc.org), and through HBP services.



**Disclosures:** **M. Puchades:** None. **G. Csucs:** None. **M. Checinska:** None. **M. Øvsthus:** None. **I.E. Bjerke:** None. **K. Andersson:** None. **T.B. Leergaard:** None. **J.G. Bjaalie:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.13/WW30

**Topic:** I.07. Data Analysis and Statistics

**Support:** Federal Ministry of Education and Research (BMBF) grants 01GQ1302 and 01GQ1509

**Title:** Formats, tools and services for efficient data management, reproducibility and collaboration in neuroscience

**Authors: A. KOUTSOU**[1], C. GARBERS[1], M. SONNTAG[1], *C. J. KELLNER[1], A. STOEWER[1], J. GREWE[2], T. WACHTLER[1]
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**Abstract:** Management of scientific data, including consistent organization and storage of data, is a challenging task. Data needs to be annotated with metadata to provide information about the underlying experiment to ensure reproducibility. Accessing and managing data from multiple workplaces while keeping it in sync, backed up, and easily accessible from within or outside the lab, is even more demanding. To minimize the time and effort scientists have to spend on these tasks, we here present formats and tools designed for comprehensive and reproducible management of scientific data. To easily store, select, retrieve and share data using an open format we provide the NIX[1] format, which offers convenient organization of data and metadata, supporting various data types including electrophysiology and imaging, and enables to effectively link data and corresponding analysis results as well as the associated metadata. NIX builds on the odML[2] metadata format and is supported by the Neo[3] Python package for electrophysiology, enabling Neo users to store their data in a common open format. Keeping data organized in the lab is made easy via the GIN[4] services. GIN keeps track of changes to the contents and organization of the files and provides secure remote access, making it convenient to work from multiple workplaces while keeping all data available and in sync. Data can be managed from web and file browsers or through a command line interface, enabling even integration into data acquisition and analysis procedures. The system works with any kind of directory structure and file types, using established technologies to keep previous versions accessible when datasets are updated. The service furthermore makes it straightforward to share data within a lab or with off-site collaborators and to work on it together. Any data hosted with the service can easily be made persistently available with digital identifiers for publication.

Combining GIN and NIX allows streamlining data workflows and eases the sharing of well-annotated datasets within the lab, among collaborators between labs, or with the public.
[1] http://www.g-node.org/nix/
[2] http://www.g-node.org/odml/
[3] http://neuralensemble.org/neo/
[4] https://gin.g-node.org/

**Disclosures:** **A. Koutsou:** None. **C. Garbers:** None. **M. Sonntag:** None. **C.J. Kellner:** None. **A. Stoewer:** None. **J. Grewe:** None. **T. Wachtler:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.14/WW31

**Topic:** I.07. Data Analysis and Statistics

**Support:** NIH Grant U01NS090501

**Title:** Towards real-time, online spike sorting for large-scale extracellular recordings

**Authors: B. LEFEBVRE**, G. SPAMPINATO, E. ESPOSITO, H. KHABOU, M. STIMBERG, D. DALKARA, J. DUEBEL, *O. MARRE, P. YGER
Inst. de la Vision, Paris, France

**Abstract:** Understanding how assemblies of neurons encode information requires recording of large populations of cells in the brain. In recent years, multi-electrode arrays and large silicon probes have been developed to record simultaneously from thousands of electrodes packed with a high density. These new devices challenge the classical way to perform spike sorting. We recently developed a fast and accurate spike sorting algorithm (available as an open source software, called SpyKING CIRCUS), validated both with *in vivo* and *in vitro* ground truth experiments. The software, performing a smart clustering of the spike waveforms followed by a greedy template-matching reconstruction of the signal, is able to scale to up to 4225 channels in parallel, solving the problem of temporally overlapping spikes. It thus appears as a general solution to sort spikes from large-scale extracellular recordings.
Here we aim at implementing this algorithm in an “online” mode, sorting spikes in real time while the data are acquired, to allow closed-loop experiments for large-scale extracellular recordings. Template corresponding to the different cells were extracted and tracked over time to take into account progressive drifts in the extracellular waveform associated with each cell. We built a robust architecture for distributed asynchronous computations. Our software is parallelized to use optimally the computing resources: all the different processing steps of the algorithms can be distributed across different nodes. Our software is therefore a promising

solution for future closed-loop experiments involving recordings with hundreds of electrodes. We are currently testing the performance of the algorithm on various ground truth datasets.

**Disclosures:** **B. Lefebvre:** None. **G. Spampinato:** None. **E. Esposito:** None. **H. Khabou:** None. **M. Stimberg:** None. **D. Dalkara:** None. **J. Duebel:** None. **O. Marre:** None. **P. Yger:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.15/WW32

**Topic:** I.07. Data Analysis and Statistics

**Title:** Assessing cluster tendency in neuronal spike waveform data

**Authors: *S. MAHALLATI**[1,2], J. C. BEZDEK[4], M. R. POPOVIC[2,5], T. A. VALIANTE[6,3]
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**Abstract:** Recording of extracellular action potentials generated by spiking neurons (units) is one of the cornerstones of understanding brain microcircuit function in vivo and in vitro. Inferences about network activity can be made by identifying coincident activity and other temporal relationships among different units. However, distinguishing the number of units present within recordings from a single electrode remains a fundamental technical issue. The first step in identifying distinct units begins by clustering unlabeled spike trains with any of unsupervised learning algorithms such as c-means, single linkage, or Gaussian mixture decomposition, that all require one of two approaches: specification of a fixed value of c, the number of clusters to seek; or generation of candidate partitions for several possible values of c, followed by selection of a best candidate based on various post-clustering validation criteria. In this work, we explore the use of a pre-clustering method *improved Visual assessment of Clustering Tendency* (iVAT) to estimate the number of clusters to seek prior to employing a clustering method to assign memberships. We show the need for such a strategy by using "ground truth" data from both synthetic data and simultaneous intracellular and extracellular recordings to provide labeled clusters of spike waveforms. Different combinations of randomly occurring trains of labeled waveforms of 2 or 3 units (neurons) are presented to demonstrate the inconsistency between different feature extraction techniques (e.g. Principle component analysis (PCA), and T-student stochastic neighbour embedding (t-SNE)). Projection of the data to a lower dimensional space enables visual inspection to identify potential clusters, and our examples show

that this often leads to an incorrect interpretation of the number of clusters. iVAT is based on an algorithm that enables the visualization of possible cluster structure in the data without dimensionality reduction by imaging a measure of similarity in the high dimensional space. Following application of iVAT we then compute clustering validation indices such as Dunn's index to illustrate the relationship and compatibility of the pre- and post-cluster assessments. Finally, we show that iVAT is appropriate for assessing clusters of sets of neuronal spike waveform data since: 1) iVAT enables the visualization of possible cluster structure in the data without dimensionality reduction. 2) iVAT is not computationally intensive (O(n2)) which would allow for online implementation. 3) iVAT can be used with any distance measure; and 4) this method is conceptually independent from any specific spike sorting algorithm.

**Disclosures: S. Mahallati:** None. **J.C. Bezdek:** None. **M.R. Popovic:** None. **T.A. Valiante:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.16/WW33

**Topic:** I.07. Data Analysis and Statistics

**Support:** HHMI

**Title:** Efficient deformable alignment of large EM image volumes: A matrix solver approach

**Authors: *K. KHAIRY**, G. DENISOV, S. SAALFELD
Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA

**Abstract:** Large electron microscopy image datasets are typically composed of thousands to millions of partially overlapping two-dimensional images (tiles), which must be registered into a coherent volume prior to detection of anatomical features. A common registration strategy is to find point-matches between neighboring and overlapping images pairs, followed by an estimation of optimal image deformation using a so-called solver program. Existing EM solvers are inadequate for large data volumes. In this work, an efficient and accurate matrix-based solver method is presented. A linear system is constructed that combines minimization of point-pair distances with explicit constraints in a regularization term. In absence of reliable priors for regularization, we show how to construct a rigid-model approximation to use as prior. The linear system is then solved by any of a number of available strategies. So scalability and accuracy are delegated to efficient numerical codes, leveraging hundreds of thousands of man-hours that went into developing linear system solutions. Our method has been applied to multi-terabyte electron microscopy datasets of the adult fruit fly brain

**Disclosures:** **K. Khairy:** None. **G. Denisov:** None. **S. Saalfeld:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.17/WW34

**Topic:** I.07. Data Analysis and Statistics

**Support:** NSF Grant 1631465 MR

NSERC Discovery Grant 40352 MHM

**Title:** Pre-processing methods for denoising and hemodynamic artifact estimation in wide-field optical imaging data

**Authors:** ***M. G. MOORE**[1], Z. LI[2], J. K. ABADCHI[3], M. YAN[2], M. H. MOHAJERANI[3], M. REIMERS[1]
[1]Neurosci. Program, [2]Computat. Mathematics, Sci. and Engin., Michigan State Univ., East Lansing, MI; [3]Dept. of Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada

**Abstract:** Wide-field optical mapping (WFOM) methods can resolve neurodynamics on fast time-scales over the entire surface of a rodent brain. Various fluorophores can be employed to target membrane-voltage, calcium dynamics, or neurotransmitters, with each indicator having unique signal-to-noise and time-resolution characteristics. All WFOM methods, however, are confounded by hemodynamic artifacts, which include the BOLD (Blood-Oxygen Level Dependent) signal, pulse, and breathing artifacts. These artifacts arise due to fluctuations in hemoglobin abundance and differences between the wavelength-dependant absorbence of oxygenated and de-oxygenated hemoglobin. The relative strengths of these factors depend strongly on the imaging wavelengths, as well as the dominant tissue type represented in each pixel, i.e. neuropil, arterial, venous, or capillary. We have developed a set of pre-processing algorithms based on three-dimensional total-variation denoising (TVD) and local-regression methods, which can remove optical noise and pulse/breathing artifacts, and estimate the BOLD signal. We apply our methods to a variety of data sets, and compare BOLD estimates with results from ratiometric approaches (W. Akemann et. al., J. Neurophysiol 108, 2012; M. Carandini et. al. J. Neuroscience 53, 2015; Y. Ma et. al., Phil. Trans. R. Soc. B 371, 2015). Preprocessing can have a significant effect on the results obtained by commonly used dimension-reduction algorithms, such as Principal Components Analysis (PCA) and Non-negative Matrix Factorization (NMF).

**Disclosures:** **M.G. Moore:** None. **Z. Li:** None. **J.K. Abadchi:** None. **M. Yan:** None. **M.H. Mohajerani:** None. **M. Reimers:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.18/WW35

**Topic:** I.07. Data Analysis and Statistics

**Title:** To infinity and beyond Bitcoin: Blockchain technology for beginners

**Authors: L. V. LONG**, J. H. REUSING, *S. T. MANION
Network Centric Sci., Baltimore, MD

**Abstract:** Blockchain technology is a new system of de-centralized databases that allows for sharing of data with increased security, authenticity, validation, and speed. Essentially, the individual computers running a blockchain comprise the database and are updated simultaneously every time a data point changes. Incongruence in the data (between computers) forces a pause in the blockchain until the point of divergence is identified and remedied. Originally developed for use underlying digital currencies, it is now being adapted for use in many industries, including banking establishments, military contractors, and in facilitating product sales. There is a strong role for it in research and the scientific community in general. Topics ranging from combatting fraudulent data to improved patient care will be explored further in the poster.

**Disclosures: L.V. Long:** None. **J.H. Reusing:** None. **S.T. Manion:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.19/WW36

**Topic:** I.07. Data Analysis and Statistics

**Support:** Wellcome Trust 095668

Wellcome Trust 095669

Simons Foundation (SCGB 325512)

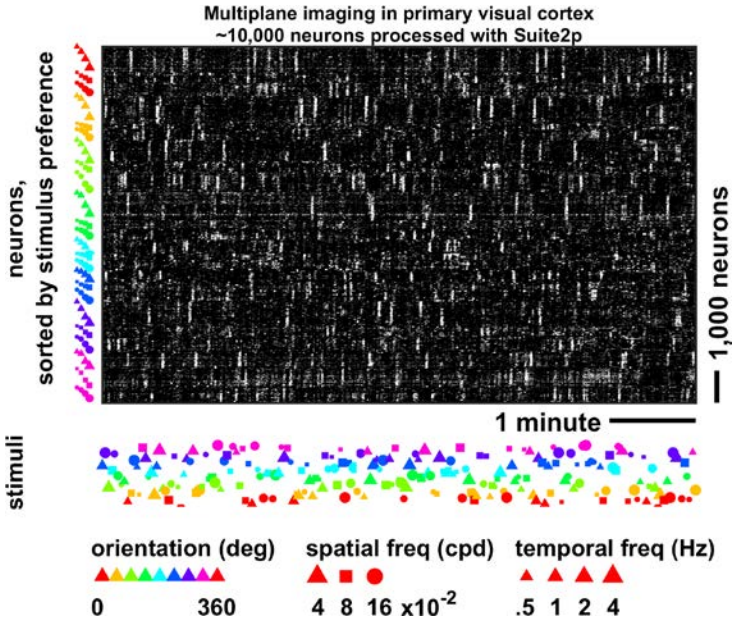
**Title:** Kilosort and Suite2p: robust and scalable frameworks for neural activity extraction in large-scale recordings

**Authors: *M. PACHITARIU**, C. STRINGER, N. STEINMETZ, S. N. KADIR, M. DIPOPPA, F. ROSSI, S. SCHRÖDER, M. CARANDINI, K. D. HARRIS
Univ. Col. London, London, United Kingdom

**Abstract:** Recent advances have greatly expanded our ability to monitor large neural populations, either by direct, dense electrical recordings or optical recordings of intracellular calcium levels. While the electrode arrays, calcium sensors and microscopes have matured over several generations of development, computational methods to process the resulting data remain inefficient. To overcome this difficulty, we developed Suite2p and Kilosort, two fast, scalable and accurate pipelines that can run on inexpensive workstation computers. To achieve this rapid processing, both pipelines take advantage of dimensionality reduction techniques, and GPU-based computing. Kilosort and Suite2p are freely available on GitHub, and are actively supported by an expanding user community.

Kilosort is a spike sorting framework that models the recorded voltage as a sum of template waveforms, allowing overlapping spikes to be identified and resolved (Pachitariu et al. bioRxiv 2016). A novel post-clustering merging step based on the continuity of the templates substantially reduces the requirement for subsequent manual curation operations. We compare Kilosort to an established algorithm on data obtained from 384-channel electrode arrays, and show superior performance, at much reduced processing times (~ real time). Kilosort is an important step towards fully automated spike sorting of multichannel electrode recordings.

Suite2p is a complete pipeline for processing 2-photon calcium imaging, that registers raw movies, detects active cells, extracts their calcium traces and infers their spike times (Pachitariu et al. bioRxiv 2016b). Suite2p runs in approximately one hour for typical two-hour long recordings, on standard workstations, and recovers ~2 times more cells than previous standard methods. The low computational load of our method allows routine detection of ~10,000 cells simultaneously from the visual cortex of awake mice with standard two-photon resonant-scanning microscopes. Recordings at this scale promise to reveal the fine structure of activity in large populations of neurons.



**Disclosures:** **M. Pachitariu:** None. **C. Stringer:** None. **N. Steinmetz:** None. **S.N. Kadir:** None. **M. Dipoppa:** None. **F. Rossi:** None. **S. Schröder:** None. **M. Carandini:** None. **K.D. Harris:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.20/WW37

**Topic:** I.07. Data Analysis and Statistics

**Support:** DARPA W911NF-09-1-0125

**Title:** The neurogram development kit: A software infrastructure for analysis of peripheral nerve neurograms

**Authors: *C. I. CONNOLLY**[1], C. BOUTON[3], S. S. CHAVAN[4], J. CORNWELL[1], P. D. LINCOLN[2], K. J. TRACEY[5], M. YADAV[2]
[2]Computer Sci. Lab., [1]SRI Intl., Menlo Park, CA; [3]Ctr. for Bioelectronic Med., The Feinstein Inst. For Med. Res., Manhasset, NY; [4]Lab. of Biomed. Sci., [5]Res. Admin., Feinstein Inst. For Med. Res., Manhasset, NY

**Abstract:** The Neurogram Deconvolution Kit (NDK) is a software suite for warehousing, compression, visualization, and analysis of local field potential recordings taken from peripheral nerves, with specific attention to Vagus nerve neurograms. NDK is built on Python and is portable to Windows, Linux, and MacOS X environments. The use of Python affords us a large degree of portability and interoperability with other languages and systems. As a partial result, NDK is able to draw on Python libraries like scikit and Theano for GPU-enabled signal processing and machine learning, and libraries like neo for interoperability with various file formats and storage schemes. NDK contains a Matlab-accessible API for performing data analysis within Matlab. The NDK is designed to accomodate a variety of signal types in both the peripheral and central nervous systems. Continuous Vagus nerve local field potential (LFP) recordings are organized into a NoSQL database system (Apache Cassandra) for efficient access to high-volume time series data. Features extracted from LFPs are organized into SQL databases (e.g. sqlite or MySQL), for representing discrete-time features and their relationships (e.g., spike clusters and behavioral events). Vagus nerve neurograms are further processed by clustering spike events to decompose the neurogram into constituent components. In many cases, multiple channel configurations provide information about the direction and speed of action potential propagation. All of these issues motivate the development within NDK of relational data models that support these needs, and the consequent use of database technology.

**Disclosures:** **C.I. Connolly:** None. **C. Bouton:** None. **S.S. Chavan:** None. **J. Cornwell:** None. **P.D. Lincoln:** None. **K.J. Tracey:** None. **M. Yadav:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.21/WW38

**Topic:** I.07. Data Analysis and Statistics

**Support:** NIH Grant NS086549

**Title:** WAVESURFER, a freely available data acquisition, signal generation, and device control software package for experimental neuroscience

**Authors: *J. M. BARRETT**[1], A. L. TAYLOR[2], L. S. LAMBOT[1], X. LI[1], H. INAGAKI[2], K. SVOBODA[2], B. KIMMEL[3], G. M. G. SHEPHERD[1]
[1]Dept. of Physiology, Feinberg Sch. of Med., Northwestern Univ., Chicago, IL; [2]Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA; [3]Vidrio Technologies, Ashburn, VA

**Abstract:** Modern neuroscientific experiments require coordinating disparate pieces of hardware, each which distinct interfaces and control software, for the collection of different signals of interest (e.g. electrophysiological, optical, behavioral) and generation of stimuli in multiple modalities (e.g. electrical, optical, auditory, tactile). One approach to achieving this is to write custom experimental control routines, but this is time-consuming, requires programming skills, and is relatively inflexible if the experimental configuration needs to be changed. WaveSurfer (wavesurfer.janelia.org) – which incorporates features of an earlier software package, Ephus (Suter et al., 2010) – represents an alternative approach. WaveSurfer coordinates electrophysiological recording & stimulation, acquisition & generation of arbitrary 1D analog signals, and triggering of external devices. WaveSurfer has a simple yet flexible user interface, which allows experiments to be reconfigured on the fly. Custom Matlab code can be invoked at different points to allow for online analysis or more sophisticated experiments, including closed-loop experiments. WaveSurfer is compatible with National Instruments X series data acquisition boards and any patch-clamp amplifier, with particular integration for Axon and Heka amplifiers. WaveSurfer can be integrated with ScanImage (Vidrio) for laser scanning microscopy and photostimulation, including two-photon imaging. Here, we demonstrate how WaveSurfer's capabilities allow it to be used in a variety of experimental configurations.
WaveSurfer can be used for slice electrophysiology to deliver arbitrary voltage or current stimuli, as well as multi-wavelength optical stimulation using LEDs or lasers. We have also used WaveSurfer for in-vivo transcranial calcium imaging combined with Micro-Manager (Edelstein et al., 2014) and Retiga 2000DC cameras (QImaging), for synchronizing optical recordings with piezoelectric tactile stimulation, and for monitoring breathing to deliver respiration-locked

optogenetic stimulation.
In conclusion, WaveSurfer is a simple yet powerful, flexible, and extensible experimental control and data acquisition program. Originally designed for slice-based electrophysiology, we are currently using it in our labs for a wide variety of neuroscientific experiments.

**Disclosures:** **J.M. Barrett:** None. **A.L. Taylor:** None. **L.S. Lambot:** None. **X. Li:** None. **H. Inagaki:** None. **K. Svoboda:** None. **B. Kimmel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vidrio Technologies, LLC. **G.M.G. Shepherd:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.22/WW39

**Topic:** I.07. Data Analysis and Statistics

**Support:** NIH Grant GM084905

NSF grant DMS-1418775

ONR MURI Grant N000141310672

**Title:** Spike sorting via source localization

**Authors:** ***P. GREENE**[1], J.-M. FELLOUS[2], K. LIN[3]
[1]Program in Applied Mathematics, [2]Dept. of Psychology; Program in Applied Mathematics, [3]Dept. of Mathematics, Univ. of Arizona, Tucson, AZ

**Abstract:** Extracellular, multi-unit recordings allow the spiking activity of multiple cells in the vicinity of a probe to be recorded in awake, behaving animals. To make use of this data, it is often necessary to perform spike detection and sorting, i.e., determine when a cell spikes and which cell was responsible for a given spike. A common method is to detect spikes by thresholding, then perform spike-sorting via, e.g., clustering or template-matching [1]. Though such methods can be made relatively fast, they have a number of known short-comings, including: (i) cells with similarly-shaped spikes can be difficult to distinguish, (ii) it can be difficult to detect and sort overlapping spikes, (iii) there is a bias for cells with larger spikes, (iv) estimating the number of cells in the recording often relies on human judgement, and (v) it is difficult to systematically quantify the uncertainty in spike assignments [2].
We propose a Bayesian framework for spike detection and sorting designed to address these issues. Building on earlier work of Mechler, Victor, and collaborators [3, 4], our method combines a dipole-based model of spiking units and a biophysical model of the source-probe transfer function, allowing explicitly for multiple spiking units at fixed but unknown locations.

We show that a version of the expectation maximization algorithm can effectively perform both spike detection and sorting. Simultaneously, our method yields rough estimates of the location of each spiking unit relative to the probe, which can be used to give a more complete picture of local spiking activity and information processing.

**References:**

[1] Rey, H.G., et al. Past, present and future of spike sorting techniques. Brain Res. Bull. 119: 106-117, 2015.
[2] Lewicki, M.S. A review of methods for spike sorting: the detection and classification of neural action potentials. Network: Comput. Neural Syst. 9: R53-R78, 1998.
[3] Mechler, F. and Victor, J. Dipole characterization of single neurons from their extracellular action potentials. J. Comput. Neurosci. 32: 73-100, 2012.
[4] Mechler, F. et al. Three-dimensional localization of neurons in cortical tetrode recordings. J. Neurophysiol. 106: 828-848, 2011.

**Disclosures: P. Greene:** None. **J. Fellous:** None. **K. Lin:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

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**Program#/Poster#:** 532.23/WW40

**Topic:** I.07. Data Analysis and Statistics

**Support:** NIH Grant R03NS091737

NIH Grant R01NS092875

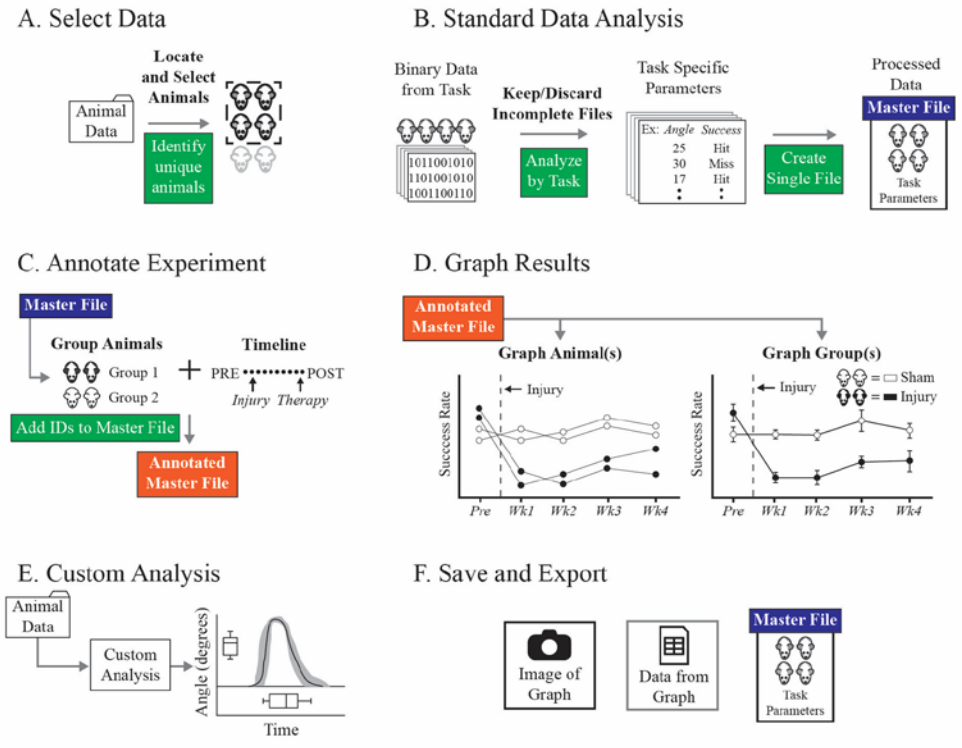
New York State Spinal Cord Injury Research Board

**Title:** Dexterity: Software for analysis and visualization of automated and manual motor tasks

**Authors: *S. D. BUTENSKY**[1], A. M. SLOAN[2], E. MEYERS[3], A. SINDHURAKAR[1], J. B. CARMEL[1]
[1]Burke Med. Res. Inst., White Plains, NY; [2]Vulintus, LLC, Dallas, TX; [3]Univ. of Texas At Dallas, Richardson, TX

**Abstract:** Hand function is critical for independence, and neurological injury often impairs dexterity. To measure hand function in people or forelimb function in animals, sensors are employed to quantify manipulation. These sensors make assessment easier and more quantitative and allow automation of these tasks. While automated tasks improve objectivity and throughput, they also produce large amounts of data that can be burdensome to analyze. We created MATLAB software called Dexterity that simplifies data analysis of both automated and non-automated forelimb tasks. Through a graphical user interface, files are loaded and data are

identified and analyzed. These data can be annotated or graphed directly. Analysis is saved, and the graph and corresponding data can be exported. For additional analysis, Dexterity provides access to custom MATLAB scripts created by other users. To determine the utility of Dexterity, we performed a study to evaluate the effects of task difficulty on the degree of impairment after corticospinal injury; the task analyzed was an automated forelimb supination task for rodents (Vulintus, Inc.). Dexterity analyzed two months of data quickly and allowed new users to annotate the experiment, visualize results, and save and export data. We also analyzed data from a non-automated task, the Vermicelli Manipulation task, and another automated task, the isometric pull task (Vulintus, Inc.) before and after motor cortex lesion. Dexterity made the tools required to analyze, visualize and annotate data easy to use by investigators without data science experience.




**Disclosures:** **S.D. Butensky:** None. **A.M. Sloan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vulintus, Inc.. **E. Meyers:** None. **A. Sindhurakar:** None. **J.B. Carmel:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.24/WW41

**Topic:** I.07. Data Analysis and Statistics

**Support:** NIH Grant DP1NS096787

**Title:** Automated identification of dendritic spines for live imaging

**Authors: *M. S. SMIRNOV**, R. YASUDA
Max Planck Florida Inst., Jupiter, FL

**Abstract:** Synaptic plasticity, the cellular basis for learning and memory, is mediated by a complex biochemical network of signaling proteins. These proteins are compartmentalized in dendritic spines, the tiny, bulbous, post-synaptic structures found on neuronal dendrites. The ability to screen a high number of molecular targets for their effect on dendritic spine structural plasticity will require a high-throughput imaging system capable of stimulating and monitoring hundreds of dendritic spines in various conditions. In order to screen many spines over long periods of time, reliance on human input has to be minimal. For this purpose, we present a program capable of automatically identifying dendritic spines in live, fluorescent tissue. Our software relies on a machine learning approach in order to minimize any need for parameter tuning from the user. Custom thresholding and binarization functions serve to “clean” fluorescent images, and a neural network is trained using features based on the relative shape of the spine perimeter and its corresponding dendritic backbone. Our algorithm is rapid, flexible, and has over 90% accuracy in spine detection. Furthermore, our software is built to easily interface with Scanimage, an open-source, MATLAB - based imaging suite. Therefore, we have designed a system capable of automatically identifying, imaging, and stimulating dendritic spines in live tissue.

**Disclosures: M.S. Smirnov:** None. **R. Yasuda:** None.

**Poster**

**532. Software Tools I**

**Location:** Halls A-C

**Time:** Tuesday, November 14, 2017, 8:00 AM - 12:00 PM

**Program#/Poster#:** 532.25/WW42

**Topic:** I.07. Data Analysis and Statistics

**Title:** Inter-patient seizure classification using 1-D convolutional neural networks

**Authors: *G. CHAU**
Pontificia Univ. Catolica Del Peru, Lima, Peru

**Abstract:** Epilepsy is the fourth most common neurological disorder affecting around 50 million people worldwide (Megiddo *et al.*, 2016). The idea of automatic detection of epileptic seizures has long been researched as it can help relieve the burden of visual analysis performed manually

and can work in tandem with adaptive stimulation devices.
An extensive variety of studies in the literature has focused on patient-specific methods that are trained only with data from one specific patients (c.f. Gadhoumi *et al.* 2015 and Schoeb *et al.* 2010). However, these systems are not able to generalize well to other patients. An inter-patient seizure detection system, i.e. one that does not have to be trained individually for each new patient, is still an open topic. Some studies like Wilson *et al.* (2004), Fergus *et al.* (2014), and Thodoroff *et al.* (2016) have tried to tackle this problem, with this last one obtaining a sensitivity of 85% and a false positive rate (FPR) of 0.8/hours using a classical 2D convolutional neural network (CNN) on images projected from EEG time series data of the CHB-MIT database (Goldberger *et al.*, 2000).Here, we show that 1-D CNNs (in contrast with 2-D CNNs used by previous studies) applied directly on EEG time series may be more suitable for this classification tasks as we obtained improvements with respect to previous studies. We designed a 1-D CNN consisting of three convolutional layers and five dense layers. The convolutional filters were applied along the time dimension considering the different EEG channels as separate time series. The 1-D CNN system was tested on a subset of the CHB-MIT database consisting on EEG recordings from 23 pediatric patients. For each patient, all seizure records and an equal number of randomly selected non-seizure records were taken to form the dataset. Each recording was segmented into non-overlapping 2 second samples and labeled as positive (seizure) or negative (non-seizure) according to the provided groundtruth. A dropout value of 0.2 was added between layers to reduce risks of overfitting and class frequency loss weights were added in order to accommodate for the unbalanced number of positive and negative training samples. The 1-D CCN was trained with the stochastic gradient descent algorithm (initial learning rate: 0.01, momentum: 0.9, decay: 1E-6) over 150 epochs.
Using a leave-one-patient-out test scheme, we obtained an average sensitivity of 90%, which improves by around 5% the current state-of-the-art, while maintaining a comparable FPR of 0.8/hour.

**Disclosures:  G. Chau:** None.